Clinical significance of estrogen receptor β in breast and prostate cancer from biological aspects

Yoko Omoto and Hirotaka Iwase

Department of Breast Surgery, Tanabe Central Hospital, Kyotanabe, Japan

Correspondence
Hirotaka Iwase, Department of Breast Surgery, Graduate School of Medical Sciences, Kumamoto University, 1-1-1 Honjo, Kumamoto 860-8556, Japan. Tel: +81-96-373-5521; Fax: +81-96-373-5525; E-mail: hiwase@kumamoto-u.ac.jp

Etiology of Breast Cancer and Prostate Cancer
Breast cancer is the most threatening neoplastic disease in females; nearly 1.7 million women per year are diagnosed with it, accounting for 25% of all cancers in females worldwide. Prostate cancer is the second most frequently occurring cancer in males, with approximately 1.1 million new diagnoses per year (World Cancer Research Fund International, http://www.wcrf.org). These two leading cancers are so-called “hormone-dependent cancers”, which means that these cancers are initiated and developed by sex steroid hormones, that is, estrogens and androgens.

Androgen and AR, Estrogen and ER
Androgens include adrenal androgens and testosterone. Adrenal androgens are synthesized by the adrenal cortex and testosterone is produced in the testicles of males and the ovaries of females. 5α-Dihydrotestosterone is the most potent ligand of AR and is converted from testosterone in target tissues like prostate; it is processed for excretion by hydroxylation. One hydroxylation product, 3βAdiol, has been reported as the most likely ligand of ERβ in the prostate (Fig. 1). (1,2) Androgens are precursors of estrogens and therefore very important for ERs. Estrogens are synthesized by aromatization of androgens. The most potent ligand of ER is E2, which is synthesized from either estrone or testosterone (Fig. 1).

Breast and prostate cancers are among the most common of all cancers. They are referred to as hormone-dependent cancers, because estrogen and androgen are involved in their development and growth. The effects of these hormones are mediated by their respective receptors, estrogen receptor (ER) α and androgen receptor. Around 18 years ago, a second ER, ERβ, which has a very similar structure to ERs, was discovered. Its function has been investigated using a variety of methods and biological systems, leading to our present understanding that ERβ can interact with or inhibit ERα and androgen receptor function directly and/or indirectly, suppress cell growth, and influence responsiveness to endocrine therapy. In order to apply the “inhibition of cell growth” function to cancer treatment, several specific ERβ agonists have been synthesized and are being tested for effectiveness in cancer treatment. We need to keep our eyes on ERβ.

Two forms of ER: ERα and ERβ
The first estrogen receptor, ERα, was cloned from the MCF-7 human breast cancer cell line in 1985, (3) and the second estrogen receptor, ERβ, was discovered in rat prostate in 1996. (4) Estrogen receptor α is expressed mainly in sex organs, that is, breast, uterus, ovary, testis, and epididymis, but also in other organs, for example, liver, kidney, adrenal glands, pituitary gland, and hypothalamus. Expression of ERβ is not predominantly in sex organs except prostate; it is found in skin, bone, brain, lung, urinary bladder, blood vessels, lymphocytes, and fat tissues and appears to be widely distributed throughout the whole body. (5)

The structure of ERβ is homologous to that of ERα. The DNA-binding domain of ERβ is 96% conserved compared to

Key words
Breast cancer, estrogen receptor alpha, estrogen receptor beta, hormone therapy, prostate cancer

Funding Information
Ministry of Education, Culture, Sports, Science and Technology of Japan (#26461952). (#2459191000).
Received September 29, 2014; Revised December 4, 2014; Accepted January 13, 2015
Cancer Sci 106 (2015) 337–343
doi: 10.1111/cas.12613
ERα, and the ligand-binding domain shows 58% conserved residues, (5) suggesting that while ERβ could bind the same target genes as ERα, it might have different specific ligands (Fig. 2). With E2 bound, helix 12 of the receptor is exposed and binds cofactor proteins, but with other ligands, different cofactors may be recruited, leading to activation of different downstream genes.

Estrogen receptor has been shown to bind to AP1 or specificity protein 1 without dimerization, (7) and thus can activate transcriptional effects at AP1 sites when complexed with E2. (8,9) Estrogen receptor has been shown to bind to AP1 or specificity protein 1 without dimerization, (7) and thus can activate transcriptional effects at AP1 sites when complexed with E2. (8,9) It suggested that ERα and ERβ have opposite transcriptional effects at AP1 sites when complexed with E2.

**Estrogen receptor β variants.** Multiple variant forms of ERβ were detected in 1998. (10) The most significant form was named ERβ2 (or ERβcx). Estrogen receptor β2 was cloned as full-length cDNA and had identical DNA binding domains, however, its ligand affinity is apparently different. In rodents, an ERβ isoform named ERβins has been described which contains a 54-nt insertion in the ligand-binding domain and shows reduced affinity for estrogens. (11,12) ERβ2 and ERβins are different forms but might have the same function in different species.

Both ERα and ERβ1 require ligand binding, and ERβ1 can form homodimers as well as ERα–ERβ1 heterodimers on ERE. However, ERβ2 was found to form heterodimers with ERα or ERβ1 without ligand binding (10,13) and inhibit ERE binding of ERβ1 or ERα (Fig. 2b). Therefore, ERβ2 is functional modulators of ERα and ERβ1.

Estrogen receptor β has a somewhat lower E2 binding affinity than ERα: the Kd values of E2 calculated from saturation curves are 0.06 nM for ERα and 0.24 nM for ERβ. (5) Estrogen receptor β can bind other ligands with rather higher affinity than ERα, for example, 4-hydroxytamoxifen, the phytoestrogen genistein, and, testosterone derivatives, 3βAdiol.

**Estrogen Receptor in the Breast**

In the mammary glands, both ERα and ERβ are present. Expression of ERα is limited to luminal cells but ERβ is widely distributed, in both basal and luminal epithelial cells, fibroblasts, adipose cells, lymphocytes, and endothelial cells (Fig. 3). (14–16)

Estrogen receptor α is the principal receptor for estrogen function in the breast. Estrogen is essential for homeostasis of normal mammary gland, however, activation of ERα results in induction of cell cycling and stimulation of cell growth, and can result in the initiation and development of cancer. Clinically, evaluation of ERα expression in breast cancer specimens is considered essential for the choice of treatment, however, response to hormone therapy cannot be exactly predicted by ERα status.

**Function of ERβ in the Breast**

**Molecular biological studies.** In the MCF-7 breast cancer cell line, estradiol increases cell proliferation and causes the cells to form tumors in a mouse xenograft model, however, introducing ERβ into MCF-7 cells causes a reduction of...
proliferation in vitro and prevents tumor formation in response to estradiol.\(^{(17)}\) Another cell model with constitutive expression of ER\(\beta\) resulted in a significant inhibition of cellular growth compared with the mock transfected and prevented establishment and growth of tumors as s.c. xenografts in immunodeficient mice.\(^{(18)}\) The other xenograft model using the ER\(\alpha\)-positive breast cancer cell line T-47D in which ER\(\beta\) expression was controlled through the Tet-off system also showed that ER\(\beta\) reduced tumor growth by decreasing expression of vascular endothelial growth factor and platelet-derived growth factor \(\beta.\)^{19,20} The mechanism of growth inhibition was reported to be a retardation of transition into the S-phase of the cell cycle,\(^{(18)}\) and reduced cyclin D1 expression, frequently leading to G\(_1\) arrest.\(^{(20)}\) Microarray analysis in ER\(\beta\) stably transfected T-47D cells showed that ER\(\beta\) overexpression specifically downregulated major DNA replication and cell cycle-related genes.\(^{(21)}\) In MCF-7 cells, ER\(\beta\) was found to inhibit proliferation by repressing c-myc, cyclin D1, and cyclin A gene transcription, and increasing the expression of p21 and p27, leading to G\(_1\) cell cycle arrest (Fig. 4a).\(^{(17)}\)

**Animal studies.** A study using rat mammary glands revealed that ER\(\beta\) was expressed in 60–70% of cells at all stages of development, however, 90% of ER\(\beta\)-expressing cells did not express proliferation markers.\(^{(22)}\) The generation of BERKO mice has revealed that mammary gland development, for example, ductal elongation and lobular formation, is the same in BERKO and wild-type mice.\(^{(14)}\) However, BERKO shows reduced levels of adhesion molecules, that is, E-cadherin, connexin 32, occludin, and integrin \(\alpha\)2 (Fig. 4b), and increased cell proliferation, indicating a role for ER\(\beta\) in the final terminal differentiation of the mammary gland.\(^{(23)}\)

**Clinical studies.** Many studies have examined the association of ER\(\beta\) mRNA or protein expression with clinical parameters of breast cancer. Although this is still a matter of controversy, most reports have shown that higher expression of ER\(\beta\)1 is significantly correlated with good prognosis, and expression tends to decrease during progression.\(^{(24–27)}\) Estrogen receptor \(\beta\) agonist was reported to prevent ductal carcinoma in situ from invasive change.\(^{(27)}\) A multivariate analysis of 442 invasive breast cancers with adjuvant tamoxifen revealed that ER\(\beta\)1 status emerged as an independent predictor of recurrence and mortality, especially in a population with triple negative cancers.\(^{(26)}\) In several studies on its interaction with tamoxifen, higher ER\(\beta\) expression was an independent predictor of better response.\(^{(26,28,29)}\) Overexpression of ER\(\beta\)1 was also associated with increased sensitivity to 4-hydroxytamoxifen.\(^{(30)}\) A study of ER\(\alpha\)-positive breast cancer patients who had been treated with neoadjuvant hormone therapy found that ER\(\beta\) mRNA was neither independently predictive of response to preoperative toremifene nor improved predictions based on ER\(\alpha\) mRNA levels, which are positively correlated with response.\(^{(31)}\)

**Estrogen Receptor \(\beta\)2**

From a clinical point of view, it would be interesting if ER\(\beta\)2 could affect the sensitivity to hormone treatment of ER\(\alpha\)-positive breast cancer. There have been several reports about the relationship between ER\(\beta\)2 and tamoxifen treatment but the results are conflicting. For example, ER\(\beta\)2 protein expression was reported to be a good predictive marker for endocrine therapy,\(^{(32)}\) and ER\(\beta\)2 mRNA to be independently predictive of tamoxifen treatment outcome in ER\(\alpha\)-positive tumors,\(^{(33)}\) but a more detailed study suggested that expression of ER\(\beta\)2 in primary lesions correlated with a poor response to tamoxifen, especially in cancers with a low Allred score for progesterone receptor.\(^{(34)}\) In summary, ER\(\beta\)1 or ER\(\beta\)2 appear to interfere with ER\(\alpha\) function and downregulate ER\(\alpha\) downstream genes. Therefore, the presence of ER\(\beta\)1 or ER\(\beta\)2 could affect the sensitivity to drugs that directly bind ER\(\alpha\), that is, tamoxifen or raloxifene.

**Estrogen Receptors in the Prostate**

As a male sex-accessory tissue, the prostate has been regarded as androgen-regulated, with AR considered as the hormone receptor responsible for the regulation of prostatic growth. Testosterone is produced in and secreted by the testis and is converted into DHT in androgen-responsive tissue such as the prostate and it elicits cell growth and proliferation as well as cancer development. Therefore, a traditional therapy for prostate cancer has been androgen ablation, by castration, administration of estrogenic agents like diethylstilbestrol to suppress androgen production indirectly by the hypothalamo-pituitary-gonadal axis, use of gonadotropin-releasing hormone agonists to downregulate the pituitary or use of AR antagonists.\(^{(35–37)}\)
Estrogen receptor α exists in stroma and is very important for prostate development, and it appears in ductal epithelial cells in very short time when it is necessary for ductal branching. However, it is rarely present in the adult prostate, in which ERβ is the most abundant ER. The latter is strongly expressed in the basal and secretory compartments of benign prostate epithelium as well as in the stroma and the infiltrating immune cells.

**Association of ERα and ERβ in human prostate cancer.** Estrogen receptor β exists in some prostate cancer cell lines, but not ERα. Using an adenoviral delivery system to induce ERβ expression in prostatic cancer cells, it was shown that ERβ has antiproliferative, anti-invasive, and pro-apoptotic effects. Another study, using xenografts of ERβ-expressing LNCap prostate cancer cells, showed that E2 treatment inhibited tumor establishment and growth. Experiments using stably transfected ERβ1 or ERβ2 in prostate cancer cell lines revealed that ERβ1 inhibits proliferation, whereas ERβ2 increases proliferation, therefore, ERβ2 is oncogenic but ERβ1 has tumor-suppressing effects.

Intensive investigation of the expression of ERs, especially ERβ and its variants, in human prostate and prostatic diseases, such as hyperplasia and prostate cancer, has shown that ERβ expression declines during hyperplastic changes and ERβ1 is lost during cancer progression, whereas its splice variant, ERβ2, is expressed in advanced prostate cancer. An association between a single nucleotide polymorphism located in the promoter region of the ERβ gene and risk of developing prostate cancer was shown in a large population-based case-control study.

This evidence highly suggested antiproliferative effects of ERβ. It has been suggested that the two ERs play opposing roles in prostate cancer: that ERα is oncogenic and promotes cell proliferation and survival, whereas ERβ is predominantly protective, being anticarcinogenic and pro-apoptotic.

**Animal models.** BERKO mice show high proliferation and high apoptosis in the epithelial cells of the ventral prostate and increased prostatic hyperplasia, indicating that ERβ1 is important for maintaining a normal prostate and for suppressing tumor growth. Activation of ERα in BERKO mice leads to aberrant proliferation, inflammation, and the development of premalignant lesions; in contrast, activation of ERβ in ERKO mice is critical in prostatic stromal–epithelial cell signaling and mediating antiproliferative effects that balance the proliferative action of androgens on the epithelium.

In another experiment, diethylstilbestrol treatment in ERKO or BERKO mice induced prostatic squamous metaplasia in WT.
and BERKO mice, but not in ERKO mice. Administration of testosterone and estrogen together to BERKO or ERKO mice showed that WT and BERKO mice developed prostatic intraepithelial neoplasia, whereas ERKO mice did not.

Aromatase knockout mice, which lack synthesis of estrogen, is a good model to evaluate the effect of endogenous estrogen. ARKO mice had reduced incidences of hyperplastic lesions. A selective ERβ agonist induces apoptosis in ARKO mouse prostate. All of these investigations showed that BERKO, which is lacking ERβ, developed induced proliferation and hyperplastic lesion in its prostate, whereas ERKO, which is lacking ERα, did not, indicating that estrogenic action to stimulate prostatic disease is ERα responsive and, in contrast, ERβ is a guard to protect prostatic disease.

**Studies of CYP7B1 and 3βAdiol.** In the prostate, the most abundant estrogen is not E2 but 3βAdiol. The enzyme CYP7B1 is responsible for the hydroxylation of 3βAdiol to Triol for excretion from the body. In a broad range of antitumor changes, including decreased proliferation of ventral prostate tissues; similar results were obtained with other isoflavones. In addition, several ERβ-selective agonists have been synthesized and used to examine the effect of ERβ stimulation. Treatment of the prostate cancer cell line DU145 with one such agonist, diarylpropionitrile, decreased cell proliferation.

**Conclusions and Future Perspectives**

It has been widely reported that incidence of both breast and prostate cancer are higher in Western populations than Asian. One possible explanation for this phenomenon is diet. Soybean products contain phytoestrogens, which are very good activators of ERβ; one such compound, genistein, was found to reduce the potential for neoplastic transformation in breast and prostate tissues; similar results were obtained with other isoflavones. In addition, several ERβ-selective agonists have been synthesized and used to examine the effect of ERβ stimulation. Treatment of the prostate cancer cell line DU145 with one such agonist, diarylpropionitrile, decreased cell proliferation. Diarylpropionitrile also prevented the development of prostatic hyperplasia and inflammation in testosterone-treated luteinizing hormone receptor knockout mice, which were lacking postnatal androgen production. Another ERβ selective agonist, 8β-VE2, was shown to reverse the hyperplasia observed in the prostates of ARko mice and induced cell death in benign prostate hypertrophy and prostate cancer. Another novel selective ERβ agonist, SERBA-1, was also reported to show beneficial effects in a benign prostate hypertrophy model. New therapies targeting ERβ seem promising.

During endocrine therapy, many cancers acquire resistance against these therapies, for example, anti-estrogen, tamoxifen, or aromatase inhibitor resistance in breast cancer and anti-androgen or flutamide in prostate cancer. Estrogen receptor β-targeting therapy can be different from ERα or AR, as ERβ needs to be stimulated whereas ERα or AR need to be inhibited. However, acquisition of resistance is the main problem during hormone treatment of hormone-dependent cancer. Mechanisms of acquisition are under investigation by gene expression analysis and some clues to close this phenomenon were revealed. One is activation of cell growth signaling other than the estrogen–ER or androgen–AR pathways, for example, the PI3K/Akt/mTOR pathways. Therefore, targeting inhibition of PI3K/Akt/mTOR pathways is applied to patients with hormone receptor-positive advanced breast cancer and showed prolongation of progression-free survival. Estrogen receptor β is the frontier of nuclear receptor transcriptional factor, which has high potential to be a target of cancer treatment. To succeed in applying ERβ-targeting therapy to breast and prostate cancer, there must be more knowledge of ERα or AR. Further investigation is still awaited.

**Disclosure Statement**

The authors have no conflict of interest.

**Abbreviations**

3βAdiol 5z-androstane-3β, 17β-diol
AP1 Activator protein 1
AR Androgen receptor
BERKO Aromatase knockout
CYP7B1 5z-androstane-3β, 17β-diol hydroxylase
DHT Dihydrotestosterone
E2 17β-estradiol
ERE Estrogen response element
ERKO ERα knockout

**References**

1 Oliveira AG, Coelho PH, Guedes FD, Mahecha GA, Hess RA, Oliveira CA. 5alpha-androstane-3beta,17beta-diol (3beta-diol), an estrogenic metabolite of 5alpha-dihydrotestosterone, is a potent modulator of estrogen receptor beta gene expression in the ventral prostatic adult rat. *Steroids* 2007; 72: 914–22.

2 Weihua Z, Lathe R, Warner M, Gustafsson JA. An endocrine pathway in the prostate, ERβA, AR, 5z-androstane-3β,17β-diol, and CYB5B1, regulates prostate growth. *Proc Natl Acad Sci U S A* 2002; 99: 13589–94.

3 Beekman JM, Allan GF, Tsai SY, Tsai MJ, O’Malley BW. Transcriptional activation by the estrogen receptor requires a conformational change in the ligand binding domain. *Mol Endocrinol* 1993; 7: 1266–74.

4 Walter P, Green S, Greene G et al. Cloning of the human estrogen receptor cDNA. *Proc Natl Acad Sci U S A* 1985; 82: 7889–93.

5 Kuiper GG, Enmark E, Pelto-Huikko M, Nilsson S, Gustafsson JA. Cloning of a novel receptor expressed in rat prostate and ovary. *Proc Natl Acad Sci U S A* 1996; 93: 5925–30.

6 Porter W, Saville B, Hoivik D, Safe S. Functional synergy between the transcription factor Sp1 and the estrogen receptor. *Mol Endocrinol* 1997; 11: 1569–80.

7 Superti-Furga G, Bergers G, Picard D, Busslinger M. Hormone-dependent transcriptional regulation and cellular transformation by Fos-steroid receptor fusion proteins. *Proc Natl Acad Sci U S A* 1991; 88: 5114–8.

8 Pacek K, Webb P, Kuiper GG et al. Differential ligand activation of estrogen receptors ERalpha and ERbeta at AP1 sites. *Science* 1997; 277: 1508–10.

9 Webb P, Nguyen P, Valentine C et al. The estrogen receptor enhances AP-1 activity by two distinct mechanisms with different requirements for receptor transactivation functions. *Mol Endocrinol* 1999; 13: 1672–85.

10 Ogawa S, Inoue S, Watanabe T et al. Molecular cloning and characterization of human estrogen receptor beta2: a potential inhibitor of estrogen action in human. *Nucleic Acids Res* 1998; 26: 3505–12.

11 Chu S, Fuller PJ. Identification of a splice variant of the rat estrogen receptor beta gene. *Mol Cell Endocrinol* 1997; 132: 195–9.

12 Petersen DN, Tkalecic GT, Koza-Taylor PH, Turi TG, Brown TA. Identification of estrogen receptor beta2, a functional variant of estrogen receptor beta expressed in normal rat tissues. *Endocrinology* 1998; 139: 1082–92.

© 2015 The Authors. Cancer Science published by Wiley Publishing Asia Pty Ltd on behalf of Japanese Cancer Association.
13 Omoto Y, Eguchi H, Yamamoto-Yamaguchi Y, Hayashi S. Estrogen receptor (ER) beta1 and ERbeta2 inhibit ERalpha function differently in breast cancer cell line MCF7. Oncogene 2003; 22: 5011–20.

14 Cheng G, Weiha Z, Warner M, Gustafsson JA. Estrogen receptors ER alpha and ER beta in proliferation in the rodent mammary gland. Proc Natl Acad Sci U S A 2004; 101: 7493–46.

15 Palmieri C, Saji H, Sakaguchi H et al. The expression of oestrogen receptor (ER)-beta and its variants, but not ERalpha, in adult human mammary fibroblasts. J Mol Endocrinol 2004; 33: 35–50.

16 Speirs V, Skliris GP, Burdall SE, Carder PJ. Distinct expression patterns of ER alpha and ER beta in normal human mammary gland. J Clin Pathol 2002; 55: 371–4.

17 Paruthiyil S, Parmar H, Kerekkate V, Cunha GR, Firestone GL, Leitman DC. Estrogen receptor beta inhibits human breast cancer cell proliferation and tumor formation by causing a G2 cell cycle arrest. Cancer Res 2004; 64: 423–8.

18 Behrens D, Gill JH, Fichtner I. Loss of tumourigenicity of stably ERbeta-transfected MCF-7 breast cancer cells. Mol Cell Endocrinol 2007; 274: 19–29.

19 Hartman J, Lindberg K, Morani A, Inzunza J, Strom A, Gustafsson JA. Estrogen receptor beta inhibits angiogenesis and growth of T47D breast cancer xenografts. Cancer Res 2006; 66: 11207–13.

20 Helguero LA, Lindberg K, Gardmo C, Schwend T, Gustafsson JA, Haldosen et al. Different roles of estrogen receptors alpha and beta in the regulation of E-cadherin protein levels in a mouse mammary epithelial cell line. Cancer Res 2008; 68: 8695–704.

21 Lin CY, Strom A, Li Kong S 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: R251.

22 Saji H, Jensen EV, Nilsson S, Rylander T, Warner M, Gustafsson JA. Estrogen receptor-alpha and beta in the rodent mammary gland. Proc Natl Acad Sci U S A 2000; 97: 337–42.

23 Forster C, Makela S, Warri A et al. Involvement of estrogen receptor beta in terminal differentiation of mammary gland epithelium. Proc Natl Acad Sci U S A 2002; 99: 15578–83.

24 Roger P, Sahla ME, Makela S, Gustafsson JA, Baldet P, Rochefort H. Decreased expression of estrogen receptor beta protein in proliferative preinvasive mammary tumors. Cancer Res 2001; 61: 2537–41.

25 Omoto Y, Kobayashi S, Inoue S et al. Evaluation of estrogen receptor beta wild-type and variant protein expression, and relationship with clinicopathological factors in breast cancers. Eur J Cancer 2002; 38: 380–6.

26 Homma N, Hori R, Iwase T et al. Clinical importance of estrogen receptor-beta evaluation in breast cancer patients treated with androgen tamoxifen therapy. J Clin Oncol 2008; 26: 3727–34.

27 Huang B, Omoto Y, Iwase H et al. Differential expression of estrogen receptor alpha, beta1, and beta2 in lobular and ductal breast cancer. Proc Natl Acad Sci U S A 2014; 111: 1933–8.

28 Hopp TA, Weiss HL, Parra IS, Cui Y, Osborne CK, Fuqua SA. Low levels of oestrogen receptor beta 2 (ER beta 2) in ERalpha-positive breast cancer: specific correlation with angiogenesis and bone metastasis genes in the prostate cancer cell line PC3. Mol Endocrinol 2012; 26: 1991–2003.

29 Pasquali D, Staibano S, Prezioso D et al. Estrogen receptor beta expression in human prostate tissue. Mol Cell Endocrinol 2001; 178: 47–50.

30 Shaaban AM, Green AR, Karthik S et al. Estrogen receptor-beta polymorphism is associated with prostate cancer risk. Clin Cancer Res 2006; 12: 1936–41.

31 Attia DM, Ederveen AG. Opposing roles of ERalpha and ERbeta in the genesis and progression of adenocarcinoma in the rat ventral prostate. Prostate 2012; 72: 1013–22.

32 Bonkhoff H, Berges R. The evolving role of oestrogens and their receptors in the development and progression of prostate cancer. Eur Urol 2009; 55: 533–42.

33 Cellhay O, Yacoub M, Irani J, Dore B, Cussaud O, Fromont G. Expression of estrogen related proteins in hormone refractory prostate cancer: association with tumor progression. J Urol 2010; 184: 2172–7.

34 Chang WY, Prins GS. Estrogen receptor-beta: implications for the prostate gland. Prostate 1999; 40: 115–24.

35 Muthusamy S, Andersson S, Kim HW et al. Estrogen receptor-beta and 17beta-estradiol-induced dehydrogenase type b, a growth regulatory pathway that is lost in prostate cancer. Proc Natl Acad Sci U S A 2011; 108: 20990–4.

36 Weiha Z, Makela S, Andersson LC et al. A role for estrogen receptor beta in the regulation of growth of the ventral prostate. Proc Natl Acad Sci U S A 2001; 98: 6330–5.

37 Omato Y, Morani A, Shin GI et al. Estrogen receptor-beta regulates epithelial cellular differentiation in the mouse ventral prostate. Proc Natl Acad Sci U S A 2004; 101: 9375–80.

38 Maks P, Lear I, Purser B et al. ER beta1 impedes prostate cancer EMT by destabilizing HIF-1alpha and inhibiting VEGF-mediated snail nuclear localization: implications for Gleason grading. Cancer Cell 2010; 17: 319–32.

39 Ricke WA, McPherson SJ, Bianco JJ, Cunha GR, Wang Y, Risbridger GP. Prostatic hormonal carcinogenesis is mediated by in situ estrogen production and estrogen receptor alpha signaling. FASEB J 2008; 22: 1512–20.

40 Prins GS, Birch L, House JF, Choi I, Katzenellenbogen B, Korach KS. Estrogen imprinting of the developing prostate gland is mediated through stromal estrogen receptor alpha: studies with alphaERKO and betaERKO mice. Cancer Res 2001; 61: 6089–97.

41 Omoto Y. Estrogen receptor-alpha signaling in growth of the ventral prostate: comparison of neonatal growth and postcastration regrowth. Endocrinology 2008; 149: 4421–7.

42 Horvath LG, Henshall SM, Lee CS et al. Frequent loss of estrogen receptor-beta expression in prostate cancer. Cancer Res 2001; 61: 5331–5.

43 Hossain GS, Birch L, Nobel C. Inducible upregulation of estrogen receptor expression in the developing and adult rat prostate lobes. Endocrinology 1997; 138: 1801–9.

44 Omoto Y, Imamov O, Warner M, Gustafsson JA. Estrogen receptor alpha and imprinting of the neonatal mouse ventral prostate by estrogen. Proc Natl Acad Sci U S A 2005; 102: 1484–9.

45 Lai KM, LaSpina M, Long J, Ho SM. Expression of estrogen receptor (ER)-alpha and ER-beta in normal and malignant prostatic epithelial cells: regulation by methylation and involvement in growth regulation. Cancer Res 2000; 60: 3175–82.

46 Cheng J, Lee EJ, Madison LD, Lazennec G. Expression of estrogen receptor beta in prostate carcinoma cells inhibits invasion and proliferation and triggers apoptosis. FEMS Lett 2004; 566: 169–72.

47 Corey E, Quinn JE, Emond MJ, Buhler KR, Brown LG, Vessella RL. Inhibition of androgen-independent growth of prostate cancer xenografts by 17beta-estradiol. Clin Cancer Res 2002; 8: 1003–7.

48 Dey P, Jonsson P, Hartman J, Williams C, Strom A, Gustafsson JA. Estrogen receptors beta1 and beta2 have opposing roles in regulating proliferation and bone metastasis genes in the prostate cancer cell line PC3. Mol Endocrinol 2012; 26: 1991–2003.

49 Pasquali D, Staibano S, Prezioso D et al. Estrogen receptor beta expression in human prostate tissue. Mol Cell Endocrinol 2001; 178: 47–50.

50 Leav I, Lau KM, Adams JY 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 2000; 157: 79–92.

51 Fujimura T, Takashaki S, Urano T et al. Differential expression of estrogen receptor beta (ERbeta) and its C-terminal truncated splice variant ERbeta2 as prognostic predictors in human prostate cancer. Biochem Biophys Res Commun 2001; 289: 692–9.

52 Vellens-Karlsson C, Lindstrom S, Malmer B et al. Estrogen receptor-beta polymorphism is associated with prostate cancer risk. Clin Cancer Res 2006; 12: 1936–41.

53 Atitia DM, Ederveen AG. Opposing roles of ERalpha and ERbeta in the genesis and progression of adenocarcinoma in the rat ventral prostate. Prostate 2012; 72: 1013–22.

54 Celhay O, Yacoub M, Irani J, Dore B, Cussaud O, Fromont G. Expression of estrogen related proteins in hormone refractory prostate cancer: association with tumor progression. J Urol 2010; 184: 2172–7.

55 Chang WY, Prins GS. Estrogen receptor-beta: implications for the prostate gland. Prostate 1999; 40: 115–24.
activation of the estrogen receptor beta subtype. Cancer Res 2005; 65: 5445–53.

65 Fritz WA, Wang J, Eltoum IE, Lamartiniere CA. Dietary genistein down-regulates androgen and estrogen receptor expression in the rat prostate. Mol Cell Endocrinol 2002; 186: 89–99.

66 Lamartiniere CA, Cotroneo MS, Fritz WA, Wang J, Mentor-Marcel R, Elgavish A. Genistein chemoprevention: timing and mechanisms of action in murine mammary and prostate. J Nutr 2002; 132: 552S–8S.

67 Slater M, Brown D, Husband A. In the prostatic epithelium, dietary isoflavones from red clover significantly increase estrogen receptor beta and E-cadherin expression but decrease transforming growth factor beta1. Prostate Cancer Prostatic Dis 2002; 5: 16–21.

68 Nilsson S, Koehler KF, Gustafsson JA. Development of subtype-selective oestrogen receptor-based therapeutics. Nat Rev Drug Discovery 2011; 10: 778–92.

69 Pravettoni A, Mornati O, Martini PG et al. Estrogen receptor beta (ERbeta) and inhibition of prostate cancer cell proliferation: studies on the possible mechanism of action in DU145 cells. Mol Cell Endocrinol 2007; 263: 46–54.

70 Savolainen S, Pakarainen T, Huhtaniemi I, Poutanen M, Makela S. Delay of postnatal maturation sensitizes the mouse prostate to testosterone-induced pronounced hyperplasia: protective role of estrogen receptor-beta. Am J Pathol 2007; 171: 1013–22.

71 Dey P, Strom A, Gustafsson JA. Estrogen receptor beta upregulates FOXO3a and causes induction of apoptosis through PUMA in prostate cancer. Oncogene 2014; 33: 4213–25.

72 Toren P, Zoubeidi A. Targeting the PI3K/Akt pathway in prostate cancer: Challenges and opportunities (Review). Int J Oncol 2014; 45: 1793–801.

73 Wang LJ, Han SX, Bai E et al. Dose-dependent effect of tamoxifen in tamoxifen-resistant breast cancer cells via stimulation by the ERK1/2 and AKT signaling pathways. Oncol Rep 2013; 29: 1563–9.

74 Ciruelos Gil EM. Targeting the PI3K/AKT/mTOR pathway in estrogen receptor-positive breast cancer. Cancer Treat Rev 2014; 40: 862–71.

75 Jerusalem G, Rorive A, Collignon J. Use of mTOR inhibitors in the treatment of breast cancer: an evaluation of factors that influence patient outcomes. Breast Cancer 2014; 6: 43–57.

76 Baselga J, Campone M, Piccart M et al. Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer. N Engl J Med 2012; 366: 520–9.