Revising the role of the androgen receptor in breast cancer

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Abstract

Breast cancer (BC) is traditionally viewed as an oestrogen-dependent disease in which the androgen receptor (AR) is inhibitory, counteracting the oncogenic activity of oestrogen receptor α (ER α (ESR1)). Most probably as a result of this crosstalk, the AR has prognostic value in ER-positive disease, with AR positivity reported to correlate with a better prognosis. Activation of the AR pathway has been previously used as a therapeutic strategy to treat BC, but its usage declined following the introduction of the anti-oestrogen tamoxifen. More recently, it has been demonstrated that a subset of triple-negative BCs (molecular apocrine) are dependent upon androgen signalling for growth and therapies that inhibit androgen signalling, currently used for the treatment of prostate cancer, e.g. the antiandrogen bicalutamide and the CYP17 inhibitor abiraterone acetate are undergoing clinical trials to investigate their efficacy in this BC subtype. This review summarises the current knowledge of AR activity in BC.

Key Words

- breast cancer
- oestrogen receptor
- androgen receptors
- steroid

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Breast cancer

Breast cancers (BCs) account for one in three newly diagnosed cases of cancer in women and led to 11 600 deaths in 2010 in the UK alone (CRUK 2014). Incidence rates increased by 90% between 1971 and 2010, with the largest increase in women aged 50–69 (ONS 2013). A large proportion of this rise has been attributed to the introduction of BC screening programmes, but other factors such as changes in lifestyle are also likely to have played a role (Parkin *et al.* 2011). The disease is approximately 100 times more common in women than men, with 49 500 and 397 cases respectively diagnosed in 2010. The greatest risk factor associated with the disease after gender is age, but other risk factors such as reproductive and family histories have also been identified.

Oestrogen receptor status and BC subtypes

BCs are a highly heterogeneous disease and gene expression profiling has identified four distinct malignant subtypes termed as basal-like, human epidermal growth factor receptor 2 (HER2)-enriched, luminal A and luminal B cancers (Perou *et al.* 2000, Sørlie *et al.* 2001). This classification is based on the expression of three receptors: oestrogen receptor α (ER α (ESR1)), progesterone receptor (PR (PGR)) and the erythroblastosis oncogene B2 (ErBB2, HER2/NEU), the expression of which are predictive of clinical response and prognosis. Luminal A and luminal B subtypes account for 70% of all BCs and fall into the category of hormone-receptor-positive BCs, luminal A cancers being defined as hormone-receptor-(ER α and PR)-positive and HER2-negative while luminal B cancers are

both hormone-receptor-positive and HER2-positive. Luminal B tumours, although they show lower expression of oestrogen target genes, are more often of a high grade with a higher Ki67 index and poorer outcome compared with luminal A (Wirapati *et al.* 2008). Conversely, the HER2-enriched subtype is hormone-receptor-negative and has amplification of the oncogene *HER2/NEU*. This subtype accounts for ~20% of cases and is associated with a more aggressive disease and worse prognosis (Ross *et al.* 2009). The remaining 10% of BCs are defined as basal-like or triple-negative BCs (TNBCs), a subtype of BC defined by ER, PR and HER2 negativity. TNBC tumours have a highly varied prognosis and clinical outcome, which is probably a reflection of the number of different subgroups that have been identified through gene expression profiling (Turner *et al.* 2010, Lehmann *et al.* 2011, Turner & Reis-Filho 2013). For example, Lehmann *et al.* (2011) analysed 21 BC datasets and identified six TNBC subtypes that displayed unique gene expression profiles and ontologies: basal-like 1, basal-like 2, immunomodulatory, mesenchymal, mesenchymal stem-like and luminal androgen receptor (AR) subtypes. Interestingly, the luminal AR (molecular apocrine) subtype has been demonstrated to have a gene expression profile resembling that of ER α -positive tumours, and this signalling may be attributable to the AR (Farmer *et al.* 2005, Doane *et al.* 2006).

Management of BC

The most important prognostic and predictive factors in the management of BCs are expression of ER α , PR, HER2 and proliferation markers (e.g. Ki67), and tumour size. A small proportion (~10%) of patients present with non-invasive disease (CRUK 2014). Atypical ductal hyperplasia or ductal carcinoma *in situ* is characterised by the proliferation of malignant epithelial cells confined to the ductal system of the breast, without invasion through the basement membrane into the surrounding stroma (Page *et al.* 1985, Schnitt *et al.* 1988). Surgery followed by radiotherapy is a therapeutic option for *in situ* disease and there has been a shift from radical mastectomy towards minimally invasive procedures (Héquet *et al.* 2011). However, the majority of patients present with invasive BCs. Generally, the therapeutic strategy for invasive BCs is surgery followed by chest wall or breast irradiation. Systemic therapy is also often administered before surgery either in a neoadjuvant setting – for patients with an unfavourable tumour to breast size ratio, aiming to shrink the tumour size and achieve breast-conserving

surgery – or after surgery in the adjuvant setting. The therapeutic used is defined by molecular profiling of the tumour on an individual basis, i.e. chemotherapy or a hormonal therapy.

All patients with ER α -positive tumours are candidates for hormone therapy that either antagonises the binding of agonist ligands and/or promotes receptor degradation, through the use of anti-oestrogens, or blocks oestrogen synthesis with aromatase inhibitors (AIs). Two distinct classes of synthetic anti-oestrogens have been developed: selective ER modulators (SERMs) and selective ER down-regulators (SERDs). SERMs are a class of ER α ligands, exemplified by tamoxifen (Nolvadex), that act as either antagonists or agonists depending on tissue context (Jordan 2007), whereas SERDs (e.g. fulvestrant/Faslodex) are a class of steroidal, pure anti-oestrogens. Fulvestrant binds to ER α , induces an inactive conformation, blocking ER α dimerisation and nuclear localisation, and in addition targets ER α for ubiquitination and degradation by the proteasome (Cardoso *et al.* 2013). The use of AIs is generally restricted to postmenopausal women with ER-positive disease. In premenopausal women, oestrogen is predominantly derived from the ovaries, but post menopause oestrogen is mainly produced in the peripheral tissues of the body. AIs are used to reduce oestrogen production within the tumour and in peripheral tissues (Jordan 2007), where the aromatase enzyme converts androstenedione into oestrone and testosterone into oestradiol (E₂). This therapy is not as effective in premenopausal women as a reduction in oestrogen levels activates the hypothalamus–pituitary axis to increase gonadotrophin secretion, thus stimulating the ovaries to increase steroid production.

Patients with ER α -negative disease and HER2 amplification are usually treated with the MAB trastuzumab (Herceptin) either alone or in combination with chemotherapy (Perez *et al.* 2011). HER2, like other members of the ErbB family, is a plasma-membrane-bound receptor tyrosine kinase. HER2 homodimerisation, or heterodimerisation with other members of the family, results in autophosphorylation that subsequently initiates a number of oncogenic signalling pathways such as MAPK and PI3K/Akt. Trastuzumab binds to the extracellular domain of HER2 and inhibits proliferation through multiple mechanisms as well as targeting the cell for destruction via the immune system (Nutti *et al.* 2011). Chemotherapy is also the preferred treatment for TNBCs, although therapies targeting the AR are currently under investigation due to the increasing importance of this receptor in this subtype.

Steroid receptors

The nuclear receptors comprise one of the largest families of transcription factors, with 48 members presently described in humans (Robinson-Rechavi *et al.* 2003). The steroid receptors form a subfamily, characterised as ligand-dependent, sequence-specific transcription factors (Mangelsdorf *et al.* 1995). Upon ligand binding, the receptors regulate gene expression to control development, homeostasis and metabolism (Olefsky 2001). Like other nuclear receptors, steroid receptors have a modular structure consisting of an N-terminal activation domain, a central DNA-binding domain and a C-terminal ligand-binding domain (Brooke & Bevan 2009). The steroid receptor family comprises the AR, ER, glucocorticoid receptor (GR), mineralocorticoid receptor (MR) and PR. Two main ER variants have been described, ER α and ER β , encoded by two separate genes (*ESR1* and *ESR2*). This review will focus on ER α and AR signalling.

Androgen and ER signalling

In women, androgens are produced by the ovaries and adrenal glands and are secreted at a higher level than oestrogen (Burger 2002). The main circulating androgens in premenopausal women are DHEAS, DHEA, androstenedione, testosterone and dihydrotestosterone, with the AR only having high affinity for the latter two. In women, 50% of circulating testosterone is produced by the ovaries and adrenal gland and released directly into the blood. The remaining 50% is synthesised from adrenal androgens in other parts of the body (e.g. adipose tissue; Burger 2002). The aromatase enzyme metabolises testosterone to E₂ and androstenedione to oestrone. Oestrone can also be converted to E₂, a step metabolised by 17 β -hydroxysteroid dehydrogenase.

There are a number of similarities between the AR and ER α signalling pathways. In the absence of ligand, both receptors are held in an inactive ligand-binding competent state through association with heat shock protein complexes (Pratt & Toft 1997, Le Romancer *et al.* 2011). Upon ligand binding, the receptors undergo a conformational change that promotes nuclear localisation, dimerisation and DNA binding. Both receptors recruit a range of cofactors, some of which are common to both pathways, and the general transcription machinery to subsequently initiate transcription. Steroid receptors interact with DNA via sequence-specific hormone response elements consisting of an inverted repeat of core recognition sequence separated by 3 bp, and this is

exemplified by ER binding to an inverted repeat of 5'-AGGTCA-3' (Carroll *et al.* 2006). The AR binds to an imperfect inverted repeat of the 5'-AGAACA-3' core recognition sequence (Beato 1989, Massie *et al.* 2011), but this is not specific for the AR, as the GR, MR and PR also bind to such response elements (Glass 1994). However, response elements specific for the AR have also been identified and consist of direct repeats of the core recognition sequence (Claessens *et al.* 2001).

ER α can also regulate gene transcription without directly binding to response elements. This is achieved through interaction with transcription factors that tether the receptor to DNA (Björnström & Sjöberg 2005). For example, ER α is recruited to the BC susceptibility gene *BRCA1* via interaction with specificity protein1 (SP1) transcription factors and activator protein 1, allowing for oestrogen regulation of a target gene that lacks an oestrogen response element (ERE; Jeffy *et al.* 2005, Hockings *et al.* 2008). In addition to their genomic activity, both AR and ER α are also known to signal at the cell membrane and activate downstream signalling cascades. For example, AR and ER α can form ternary complexes with c-Src and modulator of non-genomic activity of oestrogen receptor (MNAR; Wong *et al.* 2002, Unni *et al.* 2004). Binding of the ligand to either receptor results in activation of c-Src and subsequent activation of various downstream pathways, including MAPK. This non-genomic signalling allows for a more rapid cellular response to stimuli compared with the classical pathway (Falkenstein *et al.* 2000).

AR and ER α crosstalk

Several studies have demonstrated that the AR and ER α inhibit each other's activity and that multiple mechanisms of crosstalk exist between the receptors (Fig. 1). For example, Panet-Raymond *et al.* (2000) showed that, in the presence of E₂, the N-terminus of AR can interact with the ER α LBD and that this interaction is inhibitory to the transcriptional activity of both receptors, demonstrating that direct interaction between the receptors impedes signalling. Electrophoretic mobility shift assays and chromatin immunoprecipitation studies have also demonstrated that the AR can bind to EREs (Peters *et al.* 2009). Transfection of BC cells with the AR DNA-binding domain was sufficient to inhibit ER α activity indicating that direct competition for binding sites is also a mechanism of crosstalk between the pathways. Lastly, the transcriptional activities of the AR and ER α are known to be influenced by common cofactors (reviewed in

Figure 1

Potential mechanisms of crosstalk between the androgen receptor and oestrogen receptor α pathways. (1) In classical ER α signalling, the ligand-bound receptor binds to specific DNA sequences (oestrogen response elements (EREs)) found in the regulatory regions of target genes, and via the recruitment of a complex of accessory proteins (coactivators) and the general transcription machinery, initiates gene transcription. (2) ER α also regulates gene transcription through interaction with transcription factors that tether the receptor to DNA. (3) The AR and ER α have been found to directly interact and this interaction is inhibitory to the transcriptional

activity of both receptors. (4) The AR can bind to EREs and hence there may be competition for DNA occupancy. (5) ER α and AR share common coactivator proteins and hence through sequestration of accessory proteins, the AR may reduce ER α signalling. (6) ER α also has non-genomic actions, with membrane-bound receptors able to regulate protein kinase cascades (e.g. MAPK). (7) The AR has a similar non-genomic activity and competition for accessory proteins (e.g. MNAR), important in this signalling, may inhibit receptor activity.

Risbridger *et al.* (2010)). For example ARA70, a well-known AR cofactor, can also act as an ER α coactivator and competition for such factors is likely to have a bearing on receptor signalling (Lanzino *et al.* 2005). Similarly, as described above, the AR and ER α interact with common partners to regulate signalling pathways at the cell membrane, and hence competition for scaffold proteins such as MNAR (PELP1) may regulate the non-genomic activity of these receptors.

AR in the breast

In normal breast

At birth, the mammary gland consists of a rudimentary ductal system that continues to grow in proportion to the body until puberty, when expansive growth occurs. At this stage, ER α is the key receptor regulating ductal morphogenesis, as determined by the analysis of mouse knockout models (reviewed by Macias & Hinck (2012)). Interestingly, immunohistochemistry has demonstrated that, in premenopausal women, only 10% of epithelial cells in

acini and interlobular ducts stain positive for ER α and it appears that, in response to oestrogen, these cells secrete paracrine factors that stimulate the surrounding ER-negative cells to proliferate. In contrast, a higher percentage (20%) of cells stain positive for the AR (Li *et al.* 2010) and several studies have demonstrated that the AR also plays a role in regulating normal breast development. For example, the *Ar* knockout mouse has reduced ductal branching, decreased lobuloalveolar development and fewer milk-producing alveoli in the mammary gland (Yeh *et al.* 2003). In a separate study, Peters *et al.* (2011) demonstrated that administration of 5 α -dihydrotestosterone or the antiandrogen flutamide to female mice altered mammary gland development/morphology, with stimulation of the AR pathway resulting in reduced ductal extension in animals mid-puberty. Similar results were obtained in ovariectomised rhesus monkeys, where testosterone treatment was able to inhibit E₂-induced mammary epithelial proliferation (Zhou *et al.* 2000). It therefore appears that in normal breast, AR activity is able to balance E₂-induced cell proliferation, influencing the correct development of the gland (Yeh *et al.* 2003).

AR in BC

Although ER α plays a pivotal role in driving BC growth, the most commonly expressed hormone receptor in *in situ*, invasive and metastatic BCs is the AR. The AR is present in up to 90% of primary tumours (Søreide *et al.* 1992, Hall *et al.* 1996, Park *et al.* 2010) and 25% of metastases (Gucalp *et al.* 2013) and appears to play different roles at different stages and in different subtypes of the disease. Although BCs are still classified in clinical practice based on ER α , PR and HER2 expression, as a consequence of a growing body of evidence indicating the importance of AR activity in the absence of oestrogenic signalling, Farmer *et al.* (2005) proposed reclassification of BCs into three broad subtypes based on the presence or absence of ER α and AR: luminal (ER α + AR+), basal (ER α – AR–) and molecular apocrine (ER α – AR+).

Many *in vitro* studies have investigated the clinical significance of AR expression in BCs with the aim of characterising the effects of androgen signalling upon proliferation. The majority of studies have demonstrated that AR signalling is inhibitory towards BC cell line growth (Zhou *et al.* 2000, Ortmann *et al.* 2002, Dimitrakakis *et al.* 2003, Greeve *et al.* 2004, Macedo *et al.* 2006, Cops *et al.* 2008). However, some studies have found that androgens have a pro-proliferative activity (Birrell *et al.* 1995, Maggiolini *et al.* 1999, Lin *et al.* 2009). The disparity between these studies may be due to the lack of consistency in the methodologies used to assess cell growth (e.g. cell counting, 3-[4,5-dimethylthiazol-2-yl]-2,5 diphenyl tetrazolium bromide (MTT) colorimetric assay or FACS), conditions used for cell culturing (full or hormone-depleted media), type of androgen (e.g. dihydrotestosterone or testosterone) and dose and time of stimulation (Garay & Park 2012).

AR as a prognostic factor Immunohistochemical studies have demonstrated that AR expression varies between the different subtypes, with a higher positivity in luminal A-like tumours and a lower positivity in TNBCs (Luo *et al.* 2010, Park *et al.* 2010, Loibl *et al.* 2011, Tsang *et al.* 2014). A number of studies have investigated the prognostic potential of AR expression in BCs, with the majority finding the AR to be associated with favourable clinicopathological features. In ER α -positive BCs, AR has been found to correlate with lower grade, reduced lymph node involvement and longer disease-free survival, and this correlation is proportional to the levels of AR expression (Schippering *et al.* 2006, Søiland *et al.* 2008, Castellano *et al.* 2010, Hu *et al.* 2011, Park *et al.* 2011,

Tsang *et al.* 2014). In one study, AR and ER α levels were analysed in 1467 BC tumours from postmenopausal women enrolled in the Nurses' Health Study (Hu *et al.* 2011). Of the 1164 ER-positive tumours, 88% were also positive for AR and AR positivity was associated with a 30% reduction in BC mortality. Similarly, Castellano *et al.* (2010) investigated AR expression in 953 ER-positive tumours and found that AR expression correlates with small tumour size (<2 cm) and reduced lymph node metastasis. Furthermore, AR expression was also demonstrated to be a marker of good prognosis for time to relapse and disease-specific survival (Castellano *et al.* 2010). It has been proposed that the protective effect of the AR in BCs reflects the inhibitory effect of AR on ER α activity demonstrated *in vitro*.

AR and HER2 expression have been found to correlate in BCs (Micello *et al.* 2010, Niemeier *et al.* 2010, Park *et al.* 2010). For example, Micello *et al.* (2010) found that 77% of HER2-positive tumours were AR-positive compared with 30% in the HER2-negative group. Importantly, the improved survival associated with the AR in ER α -positive tumours was only identified in HER2-positive disease while no significant difference in overall and disease-free survival was detected in HER2-negative luminal B BCs (Tsang *et al.* 2014). Previous studies have investigated the relationship between the AR and HER2 pathways and have demonstrated that hyper-activation of HER2 enhances AR activity and that AR directly upregulates HER2 gene expression in a positive feedback loop (Naderi & Hughes-Davies 2008, Chia *et al.* 2011).

The AR is expressed in 10–43% of TNBCs (McGhan *et al.* 2014), but the prognostic value of the AR in this subtype remains unclear, with some studies indicating an increased mortality (Hu *et al.* 2011), some showing no influence of AR expression (Mrklič *et al.* 2013) and some indicating a better prognosis (Robinson *et al.* 2011, He *et al.* 2012, Sutton *et al.* 2012, Tang *et al.* 2012). For example, Hu *et al.* (2011) analysed AR expression in 211 TNBC cases and found that patients with AR-positive tumours had an 83% increase in overall mortality compared with the AR-negative group; furthermore, McGhan *et al.* (2014) found AR expression to correlate with higher tumour stage and an increase in lymph node metastases. In contrast, several studies have found AR-positive TNBC patients to have a reduced proportion of lymph node metastases (Rakha *et al.* 2007, Luo *et al.* 2010, He *et al.* 2012), increased overall survival (Luo *et al.* 2010, He *et al.* 2012), lower tumour burden and favourable differentiation (Park *et al.* 2010). It is unclear as to why contradictory results have been obtained in these studies,

but this may in part be due to the variability in antibodies used and the different scoring systems (e.g. *H* score or % positivity) and cutoffs (>0 up to $\geq 10\%$) used to define AR positivity (McGhan *et al.* 2014).

Immunohistochemical detection of the AR could be a useful indicator of better prognosis and improved survival rate, particularly in ER-positive disease. Downstream targets of the AR may also be useful biomarkers for BCs, as they can be used as a measure of receptor activity. Prostate-specific antigen (PSA) is an androgen-responsive gene, serum levels of the protein product of which are used as a biomarker for the management of prostate cancer. Although generally regarded as a prostate-specific gene, low PSA expression has also been found in mammary epithelia and PSA levels have also been correlated with BCs, with PSA expression associated with early disease stage, low grade, small tumour size, ER-positive disease, reduced risk of relapse and longer survival (Yu *et al.* 1995, Mohajeri *et al.* 2011). The current tests lack the sensitivity to measure the low levels of PSA in the sera of women, however, new ultrasensitive tests are under development (Chang *et al.* 2011). Although AR and PSA expression are not routinely assessed in patients, if therapies targeting the androgen pathway are approved for clinical use for the treatment of BC, such assays will be crucial in identifying those patients most likely to benefit.

AR in molecular apocrine disease TNBC expressing AR is clinically defined as 'molecular apocrine' (Farmer *et al.* 2005). This subtype has been extensively studied *in vitro*, predominantly using the MDA-MB-453 cell line (e.g. Doane *et al.* (2006) and Robinson *et al.* (2011)). Increased androgen signalling has also been confirmed in other TNBC cell lines (e.g. GSE-10890 and E-TABM-157) and the dependence of these cell lines on AR activity for growth has been demonstrated by targeting AR with siRNA, or treatment with the antiandrogen bicalutamide (Lehmann *et al.* 2011, Robinson *et al.* 2011). Robinson *et al.* (2011) clarified the role that AR plays in ER α -negative BCs by performing chromatin immunoprecipitation (ChIP)-sequencing to map AR-binding events in the MDA-MB-453 genome. The group were able to show that, in the absence of ER α , more than half of AR-binding events in the genome map in a similar pattern to that of ER α in ER-positive cells, promoting the expression of ER α target genes. In this context the AR is capable of, at least in part, mimicking ER α in a transcriptionally active manner, stimulating an expression pattern more similar to that of ER α in MCF7 cells than the profile reported for the AR in the LNCaP prostate cancer cell line. The pioneer factor FoxA1 appears to be critical in directing the AR to target genes

(Robinson *et al.* 2011). This indicates that, in ER α -negative disease, the AR can drive tumour progression and therefore represents a therapeutic target for this subtype of BC.

AR as a therapeutic target Targeting the AR and/or androgen synthesis is the mainstay of prostate cancer therapy, as well as long-established therapeutic antiandrogens, such as bicalutamide, new therapeutics have been developed recently with the aim of overcoming drug resistance in this malignancy. Examples include abiraterone acetate, an inhibitor of androgen biosynthesis, and the second-generation antiandrogen enzalutamide (Attard *et al.* 2005, Tran *et al.* 2009). In women, antiandrogens are currently administered to treat various medical conditions attributed to aberrations in the androgen pathway (e.g. amenorrhoea, androgenic alopecia and hirsutism), and they have also been trialled for the treatment of ovarian cancer (reviewed in Karrer-Voegeli *et al.* (2009) and Papadatos-Pastos *et al.* (2011)). Similarly, the AR is also now considered as a therapeutic target for the treatment of BC, with methods to activate the receptor as a potential option for ER α -positive disease, and inhibition of the receptor as an option for molecular apocrine disease.

Androgen supplementation therapy does have anti-proliferative activity in BC patients, but it is associated with negative side effects (e.g. increased aggressive behaviour and excessive hair growth). This, as well as the demonstration that androgens can be converted to E₂ and the introduction of tamoxifen, led to androgen therapy losing popularity in the 1970s (Garay & Park 2012). However, due to the demonstration of an oncogenic role for the AR in molecular apocrine diseases, clinical trials are underway/planned to assess the potential of inhibiting androgen signalling for the treatment of this subtype. For example, Gucalp *et al.* (2013) performed a single-arm phase II study to investigate the efficacy of the anti-androgen bicalutamide in patients with AR-positive immunohistochemistry (IHC) $\geq 10\%$, ER- and PR-negative metastatic BCs. A total of 26 participants received 150 mg bicalutamide daily until disease progression. The therapy was in general well tolerated and 19% of the patients showed a 6-month clinical benefit rate (Gucalp *et al.* 2013). This therefore demonstrates that inhibiting the AR is a promising therapeutic strategy for a subset of patients. Further clinical trials are also planned to investigate the efficacy of the antiandrogen Enzalutamide (clinicaltrials.gov: NCT01889238) and the newly developed CYP17 inhibitors abiraterone acetate (NCT00755885) and orteronel (NCT01990209), for the treatment of molecular

apocrine disease, although it will be several years before the results of these studies are published.

Conclusions

A key aim of cancer research is to identify targeted therapies to allow for personalised and tailored therapeutic regimes, and biomarkers for patient stratification to improve therapy efficacy. The AR is a key regulator of BC growth, as a crosstalk inhibitor of oestrogen signalling in ER-positive disease and as an oncogenic driver of tumour growth in molecular apocrine disease and therefore represents a useful marker and therapeutic target for the management of BCs. As a result of recent advances in the field, further clinical trials targeting this pathway are planned for the near future. Should promising initial results be upheld and expanded, this will represent a breakthrough for a subset of patients who currently have limited disease management options.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the review.

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References

- Attard G, Beldegrun AS & de Bono JS 2005 Selective blockade of androgenic steroid synthesis by novel lyase inhibitors as a therapeutic strategy for treating metastatic prostate cancer. *BJU International* **96** 1241–1246. (doi:10.1111/j.1464-410X.2005.05821.x)
- Beato M 1989 Gene regulation by steroid hormones. *Cell* **56** 335–344. (doi:10.1016/0092-8674(89)90237-7)
- Birrell SN, Bentel JM, Hickey TE, Ricciardelli C, Weger MA, Horsfall DJ & Tilley WD 1995 Androgens induce divergent proliferative responses in human breast cancer cell lines. *Journal of Steroid Biochemistry and Molecular Biology* **52** 459–467. (doi:10.1016/0960-0760(95)00005-K)
- Björnström L & Sjöberg M 2005 Mechanisms of estrogen receptor signaling: convergence of genomic and nongenomic actions on target genes. *Molecular Endocrinology* **19** 833–842. (doi:10.1210/me.2004-0486)
- Brooke GN & Bevan CL 2009 The role of androgen receptor mutations in prostate cancer progression. *Current Genomics* **10** 18–25. (doi:10.2174/138920209787581307)
- Burger HG 2002 Androgen production in women. *Fertility and Sterility* **77** (Suppl 4) S3–S5. (doi:10.1016/S0015-0282(02)02985-0)
- Cardoso F, Bischoff J, Brain E, Zotano ÁG, Lück HJ, Tjan-Heijnen VC, Tanner M & Aapro M 2013 A review of the treatment of endocrine responsive metastatic breast cancer in postmenopausal women. *Cancer Treatment Reviews* **39** 457–465. (doi:10.1016/j.ctrv.2012.06.011)
- Carroll JS, Meyer CA, Song J, Li W, Geistlinger TR, Eeckhoutte J, Brodsky AS, Keeton EK, Fertuck KC, Hall GF *et al.* 2006 Genome-wide analysis of estrogen receptor binding sites. *Nature Genetics* **38** 1289–1297. (doi:10.1038/ng1901)
- Castellano I, Allia E, Accortanzo V, Vandone AM, Chiusa L, Arisio R, Durando A, Donadio M, Bussolati G, Coates AS *et al.* 2010 Androgen receptor expression is a significant prognostic factor in estrogen receptor positive breast cancers. *Breast Cancer Research and Treatment* **124** 607–617. (doi:10.1007/s10549-010-0761-y)
- Chang YF, Hung SH, Lee YJ, Chen RC, Su LC, Lai CS & Chou C 2011 Discrimination of breast cancer by measuring prostate-specific antigen levels in women's serum. *Analytical Chemistry* **83** 5324–5328. (doi:10.1021/ac200754x)
- Chia KM, Liu J, Francis GD & Naderi A 2011 A feedback loop between androgen receptor and ERK signaling in estrogen receptor-negative breast cancer. *Neoplasia* **13** 154–166. (doi:10.1593/neo.101324)
- Claessens F, Verrijdt G, Schoenmakers E, Haelens A, Peeters B, Verhoeven G & Rombauts W 2001 Selective DNA binding by the androgen receptor as a mechanism for hormone-specific gene regulation. *Journal of Steroid Biochemistry and Molecular Biology* **76** 23–30. (doi:10.1016/S0960-0760(00)00154-0)
- Cops EJ, Bianco-Miotto T, Moore NL, Clarke CL, Birrell SN, Butler LM & Tilley WD 2008 Antiproliferative actions of the synthetic androgen, mibolerone, in breast cancer cells are mediated by both androgen and progesterone receptors. *Journal of Steroid Biochemistry and Molecular Biology* **110** 236–243. (doi:10.1016/j.jsmb.2007.10.014)
- CRUK 2014 Key Facts: *Breast Cancer*. Last Accessed 1st May 2014. http://publications.cancerresearchuk.org/downloads/Product/CS_KF_BREAST.pdf
- Dimitrakakis C, Zhou J, Wang J, Belanger A, LaBrie F, Cheng C, Powell D & Bondy C 2003 A physiologic role for testosterone in limiting estrogenic stimulation of the breast. *Menopause* **10** 292–298. (doi:10.1097/01.GME.0000055522.67459.89)
- Doane AS, Danso M, Lal P, Donaton M, Zhang L, Hudis C & Gerald WL 2006 An estrogen receptor-negative breast cancer subset characterized by a hormonally regulated transcriptional program and response to androgen. *Oncogene* **25** 3994–4008. (doi:10.1038/sj.onc.1209415)
- Falkenstein E, Tillmann HC, Christ M, Feuring M & Wehling M 2000 Multiple actions of steroid hormones – a focus on rapid, nongenomic effects. *Pharmacological Reviews* **52** 513–556.
- Farmer P, Bonnefoi H, Becette V, Tubiana-Hulin M, Fumoleau P, Larsimont D, Macgrogan G, Bergh J, Cameron D, Goldstein D *et al.* 2005 Identification of molecular apocrine breast tumours by microarray analysis. *Oncogene* **24** 4660–4671. (doi:10.1038/sj.onc.1208561)
- Garay JP & Park BH 2012 Androgen receptor as a targeted therapy for breast cancer. *American Journal of Cancer Research* **2** 434–445.
- Glass CK 1994 Differential recognition of target genes by nuclear receptor monomers, dimers, and heterodimers. *Endocrine Reviews* **15** 391–407. (doi:10.1210/edrv-15-3-391)
- Greeve MA, Allan RK, Harvey JM & Bentel JM 2004 Inhibition of MCF-7 breast cancer cell proliferation by 5 α -dihydrotestosterone; a role for p21^{Cip1/Waf1}. *Journal of Molecular Endocrinology* **32** 793–810. (doi:10.1677/jme.0.0320793)
- Gucalp A, Tolaney S, Isakoff SJ, Ingle JN, Liu MC, Carey LA, Blackwell K, Ruqo H, Nabell L, Forero A *et al.* 2013 Phase II trial of bicalutamide in patients with androgen receptor-positive, estrogen receptor-negative metastatic breast cancer. *Clinical Cancer Research* **19** 5505–5512. (doi:10.1158/1078-0432.CCR-12-3327)
- Hall RE, Aspinall JO, Horsfall DJ, Birrell SN, Bentel JM, Sutherland RL & Tilley WD 1996 Expression of the androgen receptor and an androgen-responsive protein, apolipoprotein D, in human breast cancer. *British Journal of Cancer* **74** 1175–1180. (doi:10.1038/bjc.1996.513)

- He J, Peng R, Yuan Z, Wang S, Peng J, Lin G, Jiang X & Qin T 2012 Prognostic value of androgen receptor expression in operable triple-negative breast cancer: a retrospective analysis based on a tissue microarray. *Medical Oncology* **29** 406–410. (doi:10.1007/s12032-011-9832-0)
- Héquet D, Bricou A, Delpech Y & Barranger E 2011 Surgical management modifications following systematic additional shaving of cavity margins in breast-conservation treatment. *Annals of Surgical Oncology* **18** 114–118. (doi:10.1245/s10434-010-1211-0)
- Hockings JK, Degner SC, Morgan SS, Kemp MQ & Romagnolo DF 2008 Involvement of a specificity proteins-binding element in regulation of basal and estrogen-induced transcription activity of the *BRCA1* gene. *Breast Cancer Research* **10** R29. (doi:10.1186/bcr1987)
- Hu R, Dawood S, Holmes MD, Collins LC, Schnitt SJ, Cole K, Marotti JD, Hankinson SE, Colditz GA & Tamimi RM 2011 Androgen receptor expression and breast cancer survival in postmenopausal women. *Clinical Cancer Research* **17** 1867–1874. (doi:10.1158/1078-0432.CCR-10-2021)
- Jeffy BD, Hockings JK, Kemp MQ, Morgan SS, Hager JA, Beliakoff J, Whitesell LJ, Bowden GT & Romagnolo DF 2005 An estrogen receptor- α /p300 complex activates the *BRCA-1* promoter at an AP-1 site that binds Jun/Fos transcription factors: repressive effects of p53 on *BRCA-1* transcription. *Neoplasia* **7** 873–882. (doi:10.1593/neo.05256)
- Jordan VC 2007 SERMs: meeting the promise of multifunctional medicines. *Journal of the National Cancer Institute* **99** 350–356. (doi:10.1093/jnci/djk062)
- Karrer-Voegeli S, Rey F, Reymond MJ, Meuwly JY, Gaillard RC & Gomez F 2009 Androgen dependence of hirsutism, acne, and alopecia in women: retrospective analysis of 228 patients investigated for hyperandrogenism. *Medicine* **88** 32–45. (doi:10.1097/md.0b013e3181946a2c)
- Lanzino M, De Amicis F, McPhaul MJ, Marsico S, Panno ML & Andò S 2005 Endogenous coactivator ARA70 interacts with estrogen receptor α (ER α) and modulates the functional ER α /androgen receptor interplay in MCF-7 cells. *Journal of Biological Chemistry* **280** 20421–20430. (doi:10.1074/jbc.M413576200)
- Lehmann BD, Bauer JA, Chen X, Sanders ME, Chakravarthy AB, Shyr Y & Pietenpol JA 2011 Identification of human triple-negative breast cancer subtypes and preclinical models for selection of targeted therapies. *Journal of Clinical Investigation* **121** 2750–2767. (doi:10.1172/JCI45014)
- Le Romancer M, Poulard C, Cohen P, Sentis S, Renoir JM & Corbo L 2011 Cracking the estrogen receptor's posttranslational code in breast tumors. *Endocrine Reviews* **32** 597–622. (doi:10.1210/er.2010-0016)
- Li S, Han B, Liu G, Ouellet J, Labrie F & Pelletier G 2010 Immunocytochemical localization of sex steroid hormone receptors in normal human mammary gland. *Journal of Histochemistry and Cytochemistry* **58** 509–515. (doi:10.1369/jhc.2009.954644)
- Lin HY, Sun M, Lin C, Tang HY, London D, Shih A, Davis FB & Davis PJ 2009 Androgen-induced human breast cancer cell proliferation is mediated by discrete mechanisms in estrogen receptor- α -positive and -negative breast cancer cells. *Journal of Steroid Biochemistry and Molecular Biology* **113** 182–188. (doi:10.1016/j.jsbmb.2008.12.010)
- Loibl S, Müller BM, von Minckwitz G, Schwabe M, Roller M, Darb-Esfahani S, Ataseven B, du Bois A, Fissler-Eckhoff A, Gerber B *et al.* 2011 Androgen receptor expression in primary breast cancer and its predictive and prognostic value in patients treated with neoadjuvant chemotherapy. *Breast Cancer Research and Treatment* **130** 477–487. (doi:10.1007/s10549-011-1715-8)
- Luo X, Shi YX, Li ZM & Jiang WQ 2010 Expression and clinical significance of androgen receptor in triple negative breast cancer. *Chinese Journal of Cancer* **29** 585–590. (doi:10.5732/cjc.009.10673)
- Macedo LF, Guo Z, Tilghman SL, Sabnis GJ, Qiu Y & Brodie A 2006 Role of androgens on MCF-7 breast cancer cell growth and on the inhibitory effect of letrozole. *Cancer Research* **66** 7775–7782. (doi:10.1158/0008-5472.CAN-05-3984)
- Macias H & Hinck L 2012 Mammary gland development. *Wiley Interdisciplinary Reviews. Developmental Biology* **1** 533–557. (doi:10.1002/wdev.35)
- Maggiolini M, Donzé O, Jeannin E, Andò S & Picard D 1999 Adrenal androgens stimulate the proliferation of breast cancer cells as direct activators of estrogen receptor α . *Cancer Research* **59** 4864–4869.
- Mangelsdorf DJ, Thummel C, Beato M, Herrlich P, Schutz G, Umesono K, Blumberg B, Kastner P, Mark M, Chambon P *et al.* 1995 The nuclear receptor superfamily: the second decade. *Cell* **83** 835–839. (doi:10.1016/0092-8674(95)90199-X)
- Massie CE, Lynch A, Ramos-Montoya A, Boren J, Stark R, Fazli L, Warren A, Scott H, Madhu B, Sharma N *et al.* 2011 The androgen receptor fuels prostate cancer by regulating central metabolism and biosynthesis. *EMBO Journal* **30** 2719–2733. (doi:10.1038/emboj.2011.158)
- McGhan LJ, McCullough AE, Protheroe CA, Dueck AC, Lee JJ, Nunez-Nateras R, Castle EP, Gray RJ, Wasif N, Goetz MP *et al.* 2014 Androgen receptor-positive triple negative breast cancer: a unique breast cancer subtype. *Annals of Surgical Oncology* **21** 361–367. (doi:10.1245/s10434-013-3260-7)
- Micello D, Marando A, Sahnane N, Riva C, Capella C & Sessa F 2010 Androgen receptor is frequently expressed in HER2-positive, ER/PR-negative breast cancers. *Virchows Archiv* **457** 467–476. (doi:10.1007/s00428-010-0964-y)
- Mohajeri A, Zarghami N, Pourhasan Moghadam M, Alani B, Montazeri V, Baiat A & Fekhrjoui A 2011 Prostate-specific antigen gene expression and telomerase activity in breast cancer patients: possible relationship to steroid hormone receptors. *Oncology Research* **19** 375–380. (doi:10.3727/096504011X13123323849636)
- Mrklić I, Pogorelić Z, Capkun V & Tomić S 2013 Expression of androgen receptors in triple negative breast carcinomas. *Acta Histochemica* **115** 344–348. (doi:10.1016/j.acthis.2012.09.006)
- Naderi A & Hughes-Davies L 2008 A functionally significant cross-talk between androgen receptor and ErbB2 pathways in estrogen receptor negative breast cancer. *Neoplasia* **10** 542–548. (doi:10.1593/neo.08274)
- Niemeier LA, Dabbs DJ, Beriwal S, Striebel JM & Bhargava R 2010 Androgen receptor in breast cancer: expression in estrogen receptor-positive tumors and in estrogen receptor-negative tumors with apocrine differentiation. *Modern Pathology* **23** 205–212. (doi:10.1038/mod-pathol.2009.159)
- Nuti M, Bellati F, Visconti V, Napoletano C, Domenici L, Caccetta J, Zizzari IG, Ruscito I, Rahimi H, Benedetti-Panici P *et al.* 2011 Immune effects of trastuzumab. *Journal of Cancer* **2** 317–323. (doi:10.7150/jca.2.317)
- Olefsky JM 2001 Nuclear receptor minireview series. *Journal of Biological Chemistry* **276** 36863–36864. (doi:10.1074/jbc.R100047200)
- ONS 2013 Cancer Registration Statistics, England, 2011. Last Accessed 1st May 2014. http://www.ons.gov.uk/ons/dcp171778_315795.pdf.
- Ortmann J, Pifti S, Bohlmann MK, Rehberger-Schneider S, Strowitzki T & Rabe T 2002 Testosterone and 5 α -dihydrotestosterone inhibit *in vitro* growth of human breast cancer cell lines. *Gynecological Endocrinology* **16** 113–120. (doi:10.1080/713603030)
- Page DL, Dupont WD, Rogers LW & Rados MS 1985 Atypical hyperplastic lesions of the female breast. A long-term follow-up study. *Cancer* **55** 2698–2708. (doi:10.1002/1097-0142(19850601)55:11<2698::AID-CNCR2820551127>3.0.CO;2-A)
- Panet-Raymond V, Gottlieb B, Beitel LK, Pinsky L & Trifiro MA 2000 Interactions between androgen and estrogen receptors and the effects on their transactivational properties. *Molecular and Cellular Endocrinology* **167** 139–150. (doi:10.1016/S0303-7207(00)00279-3)
- Papadatos-Pastos D, Dedes KJ, de Bono JS & Kaye SB 2011 Revisiting the role of antiandrogen strategies in ovarian cancer. *Oncologist* **16** 1413–1421. (doi:10.1634/theoncologist.2011-0164)
- Park S, Koo J, Park HS, Kim JH, Choi SY, Lee JH, Park BW & Lee KS 2010 Expression of androgen receptors in primary breast cancer. *Annals of Oncology* **21** 488–492. (doi:10.1093/annonc/mdp510)
- Park S, Koo JS, Kim MS, Park HS, Lee JS, Kim SI, Park BW & Lee KS 2011 Androgen receptor expression is significantly associated with better

- outcomes in estrogen receptor-positive breast cancers. *Annals of Oncology* **22** 1755–1762. (doi:10.1093/annonc/mdq678)
- Parkin DM, Boyd L & Walker LC 2011 The fraction of cancer attributable to lifestyle and environmental factors in the UK in 2010. *British Journal of Cancer* **105** (Suppl 2) S77–S81. (doi:10.1038/bjc.2011.489)
- Perez EA, Romond EH, Suman VJ, Jeong JH, Davidson NE, Geyer CE, Martino S, Mamounas EP, Kaufman PA & Wolmark N 2011 Four-year follow-up of trastuzumab plus adjuvant chemotherapy for operable human epidermal growth factor receptor 2-positive breast cancer: joint analysis of data from NCCTG N9831 and NSABP B-31. *Journal of Clinical Oncology* **29** 3366–3373. (doi:10.1200/JCO.2011.35.0868)
- Perou CM, Sørlie T, Eisen MB, van de Rijn M, Jeffrey SS, Rees CA, Pollack JR, Ross DT, Johnsen H, Akslen LA *et al.* 2000 Molecular portraits of human breast tumours. *Nature* **406** 747–752. (doi:10.1038/35021093)
- Peters AA, Buchanan G, Ricciardelli C, Bianco-Miotto T, Centenera MM, Harris JM, Jindal S, Segara D, Jia L, Moore NL *et al.* 2009 Androgen receptor inhibits estrogen receptor- α activity and is prognostic in breast cancer. *Cancer Research* **69** 6131–6140. (doi:10.1158/0008-5472.CAN-09-0452)
- Peters AA, Ingman WV, Tilley WD & Butler LM 2011 Differential effects of exogenous androgen and an androgen receptor antagonist in the peri- and postpubertal murine mammary gland. *Endocrinology* **152** 3728–3737. (doi:10.1210/en.2011-1133)
- Pratt WB & Toft DO 1997 Steroid receptor interactions with heat shock protein and immunophilin chaperones. *Endocrine Reviews* **18** 306–360. (doi:10.1210/edrv.18.3.0303)
- Rakha EA, El-Sayed ME, Green AR, Lee AH, Robertson JF & Ellis IO 2007 Prognostic markers in triple-negative breast cancer. *Cancer* **109** 25–32. (doi:10.1002/cncr.22381)
- Risbridger GP, Davis ID, Birrell SN & Tilley WD 2010 Breast and prostate cancer: more similar than different. *Nature Reviews. Cancer* **10** 205–212. (doi:10.1038/nrc2795)
- Robinson JL, Macarthur S, Ross-Innes CS, Tilley WD, Neal DE, Mills IG & Carroll JS 2011 Androgen receptor driven transcription in molecular apocrine breast cancer is mediated by FoxA1. *EMBO Journal* **30** 3019–3027. (doi:10.1038/emboj.2011.216)
- Robinson-Rechavi M, Escriva Garcia H & Laudet V 2003 The nuclear receptor superfamily. *Journal of Cell Science* **116** 585–586. (doi:10.1242/jcs.00247)
- Ross JS, Slodkowska EA, Symmans WF, Pusztai L, Ravdin PM & Hortobagyi GN 2009 The HER-2 receptor and breast cancer: ten years of targeted anti-HER-2 therapy and personalized medicine. *Oncologist* **14** 320–368. (doi:10.1634/theoncologist.2008-0230)
- Schippinger W, Regitnig P, Dandachi N, Wernecke KD, Bauernhofer T, Samonigg H & Moinfar F 2006 Evaluation of the prognostic significance of androgen receptor expression in metastatic breast cancer. *Virchows Archiv* **449** 24–30. (doi:10.1007/s00428-006-0213-6)
- Schnitt SJ, Silen W, Sadowsky NL, Connolly JL & Harris JR 1988 Ductal carcinoma *in situ* (intraductal carcinoma) of the breast. *New England Journal of Medicine* **318** 898–903. (doi:10.1056/NEJM198804073181406)
- Søiland H, Kørner H, Skaland I, Janssen EA, Gudlaugsson E, Varhaug JE, Baak JP & Søreide JA 2008 Prognostic relevance of androgen receptor detection in operable breast cancer. *Journal of Surgical Oncology* **98** 551–558. (doi:10.1002/jso.21156)
- Søreide JA, Lea OA, Varhaug JE, Skarstein A & Kvinnsland S 1992 Androgen receptors in operable breast cancer: relation to other steroid hormone receptors, correlations to prognostic factors and predictive value for effect of adjuvant tamoxifen treatment. *European Journal of Surgical Oncology* **18** 112–118.
- Sørli T, Perou CM, Tibshirani R, Aas T, Geisler S, Johnsen H, Hastie T, Eisen MB, van de Rijn M, Jeffrey SS *et al.* 2001 Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. *PNAS* **98** 10869–10874. (doi:10.1073/pnas.191367098)
- Sutton LM, Cao D, Sarode V, Molberg KH, Torgbe K, Haley B & Peng Y 2012 Decreased androgen receptor expression is associated with distant metastases in patients with androgen receptor-expressing triple-negative breast carcinoma. *American Journal of Clinical Pathology* **138** 511–516. (doi:10.1309/AJCP8AVF8FDPTZLH)
- Tang D, Xu S, Zhang Q & Zhao W 2012 The expression and clinical significance of the androgen receptor and E-cadherin in triple-negative breast cancer. *Medical Oncology* **29** 526–533. (doi:10.1007/s12032-011-9948-2)
- Tran C, Ouk S, Clegg NJ, Chen Y, Watson PA, Arora V, Wongvipat J, Smith-Jones PM, Yoo D, Kwon A *et al.* 2009 Development of a second-generation antiandrogen for treatment of advanced prostate cancer. *Science* **324** 787–790. (doi:10.1126/science.1168175)
- Tsang JY, Ni YB, Chan SK, Shao MM, Law BK, Tan PH & Tse GM 2014 Androgen receptor expression shows distinctive significance in er positive and negative breast cancers. *Annals of Surgical Oncology* (In press). (doi:10.1245/s10434-014-3629-2)
- Turner NC & Reis-Filho JS 2013 Tackling the diversity of triple-negative breast cancer. *Clinical Cancer Research* **19** 6380–6388. (doi:10.1158/1078-0432.CCR-13-0915)
- Turner N, Lambros MB, Horlings HM, Pearson A, Sharpe R, Natrajan R, Geyer FC, van Kouwenhove M, Kreike B, Mackay A *et al.* 2010 Integrative molecular profiling of triple negative breast cancers identifies amplification drivers and potential therapeutic targets. *Oncogene* **29** 2013–2023. (doi:10.1038/ncr.2009.489)
- Unni E, Sun S, Nan B, McPhaul MJ, Cheskis B, Mancini MA & Marcelli M 2004 Changes in androgen receptor nongenotropic signaling correlate with transition of LNCaP cells to androgen independence. *Cancer Research* **64** 7156–7168. (doi:10.1158/0008-5472.CAN-04-1121)
- Wirapati P, Sotiriou C, Kunkel S, Farmer P, Pradervand S, Haibe-Kains B, Desmedt C, Ignatiadis M, Sengstag T, Schütz F *et al.* 2008 Meta-analysis of gene expression profiles in breast cancer: toward a unified understanding of breast cancer subtyping and prognosis signatures. *Breast Cancer Research* **10** R65. (doi:10.1186/bcr2124)
- Wong CW, McNally C, Nickbarg E, Komm BS & Cheskis BJ 2002 Estrogen receptor-interacting protein that modulates its nongenomic activity-crosstalk with Src/Erk phosphorylation cascade. *PNAS* **99** 14783–14788. (doi:10.1073/pnas.192569699)
- Yeh S, Hu YC, Wang PH, Xie C, Xu Q, Tsai MY, Dong Z, Wang RS, Lee TH & Chang C 2003 Abnormal mammary gland development and growth retardation in female mice and MCF7 breast cancer cells lacking androgen receptor. *Journal of Experimental Medicine* **198** 1899–1908. (doi:10.1084/jem.20031233)
- Yu H, Giai M, Diamandis EP, Katsaros D, Sutherland DJ, Levesque MA, Ragna R, Ponzzone R & Sismondi P 1995 Prostate-specific antigen is a new favorable prognostic indicator for women with breast cancer. *Cancer Research* **55** 2104–2110.
- Zhou J, Ng S, Adesanya-Famuyi O, Anderson K & Bondy CA 2000 Testosterone inhibits estrogen-induced mammary epithelial proliferation and suppresses estrogen receptor expression. *FASEB Journal* **14** 1725–1730. (doi:10.1096/fj.99-0863com)

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