EDITORIAL

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Renewed interest in the progesterone receptor in breast cancer

Elgene Lim[1], Carlo Palmieri[2] and Wayne D Tilley*[,3]

[1]Garvan Institute of Medical Research and St Vincent's Hospital, University of New South Wales, NSW, Sydney, Australia; [2]Institute of Translational Medicine, University of Liverpool, Liverpool, UK and [3]Dame Roma Mitchell Cancer Research Laboratories, School of Medicine, University of Adelaide, Adelaide, SA, Australia

The progesterone receptor (PgR), a member of the nuclear receptor family, is a well-known oestrogen receptor (ER)-regulated gene that is expressed in over two-thirds of ER-positive (ER+) breast cancers (Rakha *et al*, 2007). Progesterone receptor (PR) protein generally is assessed by immunohistochemistry at the time of diagnosis in primary breast cancers in most economically developed healthcare systems. PR is more highly expressed in the luminal A breast cancer subtype, and is associated with tumour grade, ER expression, Nottingham Prognostic Group and negative HER2 status in early breast cancer (Arpino *et al*, 2005; Braun *et al*, 2013; Purdie *et al*, 2014). Multiple studies have demonstrated the improved prognosis of PR-positive (PR+) breast cancers (Collet *et al*, 1996; Bardou *et al*, 2003; Viale *et al*, 2007; Blows *et al*, 2010; Van Belle *et al*, 2010; Purdie *et al*, 2014).

The value of PR in the selection of endocrine therapy in both the adjuvant and metastatic settings has, to date, not been demonstrated. In a meta-analysis of adjuvant tamoxifen therapy, ER status was the only factor predictive of tamoxifen benefit (Early Breast Cancer Trialists' Collaborative Group (EBCTCG) *et al*, 2011). Similarly, in a meta-analysis comparing adjuvant aromatase inhibitors (AIs) to tamoxifen, the expression of PR did not demonstrate a selective advantage of AI therapy (Early Breast Cancer Trialists' Collaborative Group (EBCTCG) *et al*, 2015). Thus, at this point, the co-expression of PR with ER does not change endocrine therapy. In metastatic breast cancer, PgR loss occurs more commonly than ESR1 and HER2 loss when compared with the primary tumour (Yeung *et al*, 2016); however, its expression in the primary tumour is not associated with a differential benefit to combined endocrine and targeted therapy with mTOR and CDK4/6 inhibitors in the metastatic setting (Baselga *et al*, 2012; Turner *et al*, 2015).

It is against this background that Campbell *et al* (2016) have reported on a retrospective study in the article accompanying this editorial, evaluating the *prognostic* significance of the average Allred score of ER and PR, which they have termed the combined endocrine receptor (CER) score, compared with ER or PR alone. In their study, ER and PR were evaluated centrally in a tissue microarray and receptor positivity classified into three groups based on the Allred score (negative <3; low 3–5; high 6–8). The Allred ER and PR scores were then reclassified into three CER groups: 0 (i.e., negative endocrine receptor status), 0.5–1.5 (impaired) and 2 (high).

A derivation cohort of 557 tumours, sampled randomly from a larger cohort of 1711 patients between 1995-8, was used to derive CER scores. The validation cohort was from 2008-9 and consisted of 455 samples. The primary outcomes were breast cancer-specific survival, time to recurrence and 5-year disease-free survival (DFS). In a multivariate analysis that included ER, PR and CER, only CER remained an independent prognostic variable for 5-year DFS, leading the authors to conclude that CER is a more powerful discriminator of patient outcome than either ER or PR alone.

There were important differences between the two cohorts. In the derivation cohort, 37% patients had an ER Allred score of <3 compared to 12% in the validation cohort, and there were fewer ER- and/or PR-negative tumours in the validation cohort. Additionally, whereas the majority of HER2+ patients in the validation cohort received trastuzumab, virtually all patients in the discovery cohort received tamoxifen monotherapy. There was a higher relative proportion of HER2 expression in the CER-negative group in the discovery cohort, at a time when HER2-directed therapy was not routinely given, which may be the major driver of the poor outcomes in the CER-negative group.

The current systemic management of early-stage ER+/HER2-negative breast cancer is limited to endocrine therapy with or without chemotherapy. The authors argue that reclassification of a small percentage of patients with ER-negative tumours as CER impaired (ER-negative/PR+) would ensure that more patients with hormone receptor-positive disease will be considered eligible for endocrine treatment. However, this only affected 1% of the validation cohort, and is in keeping with other larger studies suggesting that ER-negative/PR+ breast cancers are rare and not a reproducible subtype (Rakha *et al*, 2007; De Maeyer *et al*, 2008; Hefti *et al*, 2013). Regardless

*Correspondence: Professor WD Tilley; E-mail: wayne.tilley@adelaide.edu.au
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of how much better CER is able to prognosticate above ER and PR scores, it does not change the standard of care (i.e., endocrine therapy) for adjuvant therapy in patients with positive ER or CER scores. It is also unlikely, as suggested by the authors, that the CER score has a role in guiding the use of adjuvant chemotherapy in this group of patients, especially as the CER scores have not been validated in this context, and ER and PR are not the sole genes that would determine the benefit of adjuvant chemotherapy in this breast cancer subtype (Albain *et al*, 2009).

The CER would need to be compared to IHC4, which is another IHC-based prognostic test, and includes ER, PR, HER2 and Ki67 measurements (Cuzick *et al*, 2011). One potential advantage of the CER is that it does not involve Ki67, which has well-recognised issues of inter-observer variability, limiting its general use as a biomarker currently. Genomic tests have increasingly been used as prognostic tools in breast cancer, and many of these do include PgR as a key gene measured. As a prognostic tool, the power of the CER would need to also be compared to contemporary prognostic genomic tests such as Endopredict and Oncotype Dx (Győrffy *et al*, 2015).

There is increasing evidence that substantial crosstalk occurs between ER and PR signalling pathways, whereby the activation of one has a significant impact on the other. Importantly, when PR is activated by its native ligand in the presence of oestrogen, it interacts with ER in breast cancer cells to redirect ER chromatin binding, signifying the critical role PR plays in modulating ER action (Mohammed *et al*, 2015). Progesterone stimulation of breast cancer cells *in vitro* and *in vivo* can reprogram ER binding to thousands of new *cis*-regulatory elements, resulting in changes in gene expression profiles that culminate in cell cycle arrest. In essence, progesterone was able to redirect ER-mediated transcription via sequestration of the ER complex to inhibit breast tumour growth; this new transcriptional signature was associated with favourable patient outcomes (Mohammed *et al*, 2015). In support of this, a synthetic progestogen, R5020, inhibited oestradiol-induced proliferation of primary breast cancer samples from patient tumours cultured *ex vivo*. Progesterone inhibited oestradiol-mediated breast tumour growth in mouse xenograft, and, when combined with tamoxifen therapy, prevented tumour growth more effectively than tamoxifen alone. Importantly, increased expression of a gene signature (comprising 38 genes) derived from progesterone-stimulated ER binding conferred a good prognosis, as demonstrated when patients were stratified in the Kaplan-Meir plot based on the top and bottom 5% expression intervals for the signature in the Metabric cohort of breast cancer patients ($n = 959$) (Curtis *et al*, 2012).

The true therapeutic value of PR may be to determine which tumours are amenable to progesterone-induced PR reprogramming of ER. The vast majority of data regarding the therapeutic use of synthetic progestogens in breast cancer has come in the setting of metastatic ER+ breast cancers. The above-mentioned preclinical study suggests that progesterone treatment may also be beneficial in early breast cancer. A trial of a single injection depot progesterone before surgery for breast cancers in 976 patients demonstrated a significant improvement in survival outcomes in patients with higher-risk node-positive disease (Badwe *et al,* 2011). Interestingly, in this trial, ER and PR status did not predict benefit of such an intervention. A number of clinical trials are currently being proposed in the UK and Australia to evaluate the addition of a progestogen to existing ER-directed therapies in early-stage breast cancer. Should these studies be positive, it would add a relatively inexpensive treatment option to women with the largest subtype of breast cancer, namely hormone receptor-positive disease. These trials will enable evaluation of whether the CER score is indicative of functional sex steroid receptor crosstalk in breast cancer and is a useful biomarker to select patients who are most likely to benefit from combined progestogen and current standard-of-care ER-target therapies.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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