Editorial
The evolving role of oestrogen receptor β in clinical breast cancer
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See related research article by Novelli *et al.*, http://breast-cancer-research.com/content/10/5/R74

Abstract

Controversy surrounds the potential clinical importance of oestrogen receptor (ER)β in breast cancer, and three recent papers have sought to resolve this. In the present issue of *Breast Cancer Research* Novelli and colleagues explored the significance of ERβ1 expression in 936 breast cancer patients, and they showed diverse relationships according to lymph node status. A second paper examined 442 breast cancers in which ERβ1 was an independent predictor of recurrence, disease-free survival and overall survival. Finally a third paper showed that ERβ2 was a powerful prognostic indicator in 757 breast cancers but this was dependent on cellular location, with nuclear ERβ2 expression predicting good survival whilst cytoplasmic expression predicted worse outcome. These papers point to a clinical role for ERβ in breast cancer and shall be discussed.

Oestrogen receptor (ER)α remains the most important biomarker in breast cancer as it indicates the likelihood of patients to benefit from endocrine therapy. The discovery of ERβ over a decade ago was initially greeted with interest by the breast cancer community. Its presence indicated that ER signalling was no longer restricted to ERα, with a real possibility of using ERβ as an additional prognostic or predictive marker in breast cancer, complementing ERα. A number of studies were subsequently published, examining ERβ mRNA, protein or a combination of both – but many of these studies suffered from small sample numbers, use of poorly validated primary antibodies and failure to consider the potential importance of known ERβ isoforms. This led to conflicting results, holding back anticipated progress. As a result, a great deal of scepticism began to surround the potential importance of ERβ in breast cancer.

ERβ has recently emerged from the shadows with the concurrent publication of three papers [1-3]. These articles stand out from previous studies because they examined large numbers of breast cancers using well validated, readily available antibodies.

In the present journal, Novelli and colleagues conducted a prospective immunohistochemical study of ERβ1 in 936 breast cancers [1]. Rather than relying solely on conventional statistics to define ERβ association with clinicopathological factors, the authors used two additional statistical approaches: multiple correspondence analysis, and classification and regression tree analysis. The former approach analyses patterns of relationships of several categorical dependent variables, while the latter is a tree-building technique developed to reveal complex interactions between predictors that may be difficult to find using traditional multivariate techniques. Multiple correspondence analysis showed ERβ1 positivity was associated with more aggressive breast cancer phenotypes, namely HER2-positive tumours and triple negative/basal breast cancers that do not express ERα, progesterone receptor or HER2 – a relationship that has been observed by others [3,4] (V. Speirs, unpublished observation).

In another recent study, Honma and colleagues showed ERβ1 was an independent predictor of recurrence, disease-free survival and overall survival in 442 cases [3]. Although of mixed ER status, this cohort all received tamoxifen mono-therapy with ERα⁻ERβ1⁺ phenotype tumours having survival advantage [3]. This observation suggests that the presence of any ER subtype, provided it is capable of binding ligand, can modulate an endocrine response.

The axillary lymph node status is an important prognostic factor in invasive breast cancer. Accordingly, Novelli and colleagues stratified their cohort into positive and negative lymph node status and examined the influence of ERβ1 expression on outcome in each cohort [1]. Using the classification and regression tree approach and validation by conventional statistics, ERβ1 expression predicted a high risk of relapse in the lymph node-positive group. At first glance these data might seem counterintuitive, given the general consensus that ERβ1 is a good prognostic factor in breast

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ER = oestrogen receptor.

cancer [3,5,6]. The study of Novelli and colleagues differs from most others, however, in that these patients were treated with adjuvant chemotherapy, whereas others have primarily studied patients receiving endocrine therapy. In lymph node-negative cases, by contrast, ERβ1 predicted a favourable response to endocrine therapy. These data are important; although positive node status predicted worse prognosis, some 30% of node-negative patients go on to experience relapse – an identification, therefore, of the need for potential prognostic factors in lymph node-negative cases. ERβ1 may fulfil a role in this regard.

Finally, it is important to highlight the role of cytoplasmic ERβ in dictating breast cancer outcome, something that has been consistently noted in many studies [2,3,7-9]. Shaaban and colleagues incorporated this into their immunohistochemical evaluation of ERβ1, ERβ2 and ERβ5 in 757 breast tumours [2]. In contrast to Novelli and colleagues [1] and Honma and colleagues [3], ERβ$_2$ was the most significant ERβ isoform in terms of breast cancer outcome, as it was predictive of disease-free survival, overall survival and response to hormone therapy. This group also formally examined the presence of cytoplasmic ERβ immunoreactivity. Intriguingly, the cellular location of ERβ2 determined outcome – with nuclear ERβ2 predicting good clinical response, while cytoplasmic ERβ2 expression predicted significantly worse overall survival. This was confirmed in 322 independent cases.

These studies put ERβ firmly back into the spotlight as a potentially important player in ER signalling and hormone-dependent cancer, with not only specific ERβ isoforms determining outcome but also their precise cellular location. ERβ isoforms should now be considered in translational arms of breast cancer trials where their potential clinical role can be addressed more rigorously.

Competing interests
The author declares that they have no competing interests.

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