Not enough evidence to include *ESR1* amplification

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In our recent Review (The different roles of ER subtypes in cancer biology and therapy. *Nature Rev. Cancer* **11**, 597–608 (2011))¹, we address the mechanisms that regulate the cellular levels of oestrogen receptors (ERs). We thank Yu *et al.* for their correspondence on our article², in which we focus on the role of the transcriptional regulation of ERs, including the hypermethylation of ER promoters, the post-transcriptional regulation by microRNAs and proteasome-mediated degradation of ERs. Alteration of ER levels by these mechanisms has been reported to be a common event in a number of cancers (such as in breast, prostate, colon and gynaecological cancers). In addition, the contribution of these mechanisms to the regulation of the ER levels in cancer has been validated in different systems (specimens from human subjects, and animal and cell-based studies) by using different methods^{3–6}.

In their correspondence, Yu *et al.* indicate that the mechanism of *ESR1* amplification, which is not mentioned in our Review, deserves to be discussed when illustrating the mechanisms of ERα upregulation. To support this, they discuss the results from several studies, including that of Holst *et al.*⁷, which reported that amplification of *ESR1*, as detected by fluorescence *in situ* hybridization (FISH), occurs in a substantial proportion of breast cancers (20.6%). Holst *et al.*⁷ also found that *ESR1* amplification predicts a better response to tamoxifen therapy in a subset of individuals with breast cancer⁷. However, several groups have challenged

these results, and, by using a variety of methods including comparative genomic hybridization (CGH), FISH and quantitative PCR, have shown a low frequency of *ESR1* amplification in breast cancers (two studies reported *ESR1* amplification in 1%, and less than 1%, of breast cancers)^{8–11}. Interestingly, in one of these studies, *ESR1* amplification did not show any significant correlation with ERα expression¹⁰. More recent studies have produced contradictory data with regard to the frequency of *ESR1* amplification (different *ESR1* amplification frequencies have been detected with different techniques) and have questioned its clinical significance for breast and other types of cancer¹². Consistent with the data from the majority of the previous studies, Moelans *et al.*¹³ have recently shown that *ESR1* amplification is a rare event in breast cancer. In contrast to the findings by Holst *et al.*⁷, Nielsen *et al.*¹⁴ suggested that *ESR1* amplification is associated with increased tamoxifen resistance in ERα-positive breast cancers. Together, these results, which have been derived from several institutions, have not validated previous findings of high-frequency *ESR1* amplification in cancer⁷ and conclude that *ESR1* amplification in breast cancer is an uncommon event of unknown clinical importance.

Taking these data into consideration in our Review, we avoided including *ESR1* amplification in the list tabulating important and well-validated mechanisms that are responsible for changes in ER levels and activities in cancer cells and tissues.

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Competing interests statement

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