Human invasive breast cancers (IBCs) are categorized in many ways, including on the basis of whether the tumour cells express oestrogen receptor (ER)-α. ER status is important clinically because ER mediates the growth-stimulating effects of circulating oestrogen and because tumours expressing ER have a significant chance of responding to hormonal therapies such as tamoxifen and aromatase inhibitors [1].

Epithelia in the normal breast nearly always contain a subpopulation of ER-expressing cells [2,3]. The proportion of positive cells is regulated physiologically and varies considerably with menstrual status, averaging about 30% overall [3]. About 75% of IBCs also contain a widely variable proportion of ER-positive cells [1]. In contrast, the remaining approximately 25% of IBCs do not contain any ER-positive cells [1]. The origins of these entirely ER-negative tumours have been the topic of considerable debate. Although there is no consensus, the majority opinion on this issue appears to be that ER-negative IBCs evolve from ER-negative precursors, whereas ER-positive IBCs evolve from ER-positive precursors [4]. Many observations and assumptions support the majority opinion, especially the following. First, studies have suggested that tamoxifen prevents only ER-positive IBCs in high-risk women [5]. Second, there is speculation that oestrogen must contribute to the aetiology of all breast cancers, including those that are ER-negative. Looked at from the opposite direction, decreased oestrogen exposure associated with prophylactic oophorectomy in BRCA1 mutation carriers dramatically decreases the risk for breast cancer, independent of ER status [12].

Histopathological studies also support the origin of ER-negative IBCs from ER-positive precursors. For example, nearly all well established premalignant lesions in the breast are strongly ER positive [13], including atypical ductal hyperplasia, and studies have shown that atypical ductal hyperplasia is a strong risk factor for development of IBCs independent of biological characteristics such as ER status [14]. Furthermore, the proportions of ER-positive and ER-negative IBCs decrease and increase with time, respectively. This is consistent with progression of the latter from the former. Perhaps the best illustration of this is the dramatic decrease in ER-negative breast cancer since the introduction of screening mammography (specifically, because of early detection) [15,16]. Similarly, the proportion of ER-negative tumours is substantially greater among large as compared with small IBCs, and all large tumours were smaller at an earlier point in time [16-19].

Although it is not widely appreciated, there is also considerable intratumour histological and biological diversity in breast cancers, arguing that ER-negative IBCs may evolve from ER-positive precursors. For example, the majority of IBCs appear to evolve from advanced precursor lesions,
referred to as ductal carcinoma in situ (DCIS). The latter are ER-positive in about 5% of ER-negative IBCs [20], which is consistent with the idea that ER expression is suppressed during tumour progression. Interestingly, the opposite is almost never observed. Similarly, up to 20% of metastases associated with ER-positive primary IBCs are ER negative, which again is consistent with the idea that ER expression is downregulated during tumour progression [21,22]. Recent studies also show that the majority of DCISs contain cells of diverse histological grades within individual tumours, and that ER expression significantly decreases as grade increases in these cells (as they become more poorly differentiated) [23]. In fact, most DCISs contain intratumour diversity for many features, including histological grade, standard prognostic biomarkers and even intrinsic subtypes, which is also probably true for IBCs [23]. Presumably, these areas of intratumour diversity compete for dominance, and eventually the most aggressive prevail, which is a general mechanism by which poorly differentiated (ER-negative) may gradually evolve from well differentiated (ER-positive) tumours.

Several molecular mechanisms have recently been identified, which may be involved in the loss of ER expression during tumour progression. For example, recent studies have demonstrated that hypermethylation of the ER promoter can reversibly downregulate ER expression in IBCs [24]. Other recent studies have shown that activation of the mitogen-activated protein kinase pathway, especially through ligand-activated tyrosine kinase receptors at the cell surface, can downregulate ER expression in a reversible manner [25]. There is some evidence that even apparently normal physiological responses retained by tumour cells can result in ER-negative IBCs. For example, so-called apocrine metaplasia is a common phenomenon in all types of benign breast epithelia, and it is associated with a complete loss of ER expression [26]. Apocrine metaplasia is also commonly observed in breast cancers [26,27] and may be responsible for the development of a substantial proportion of ER-negative disease in a potentially reversible manner.

Overall, the evidence appears overwhelming that many ER-negative IBCs evolve from ER-positive precursors, although it also seems likely that some ER-negative IBCs may also evolve from ER-negative precursors. Finding effective therapies for these diverse types of ER-negative breast cancers will be dependent on a comprehensive understanding of the mechanisms that are responsible for their development, and there are likely to be many.

Acknowledgement
This article has been published as part of Breast Cancer Research Volume 9 Supplement 2, 2007: Controversies in Breast Cancer. The full contents of the supplement are available online at http://breast-cancer-research.com/supplements/9/S2.

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