Letter

Luminal B breast tumors are not HER2 positive

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We read with interest the article by Tamimi and coworkers recently published in this journal [1]. The authors compared the molecular subtypes of invasive carcinoma versus ductal carcinoma *in situ* and found significant differences, as expected [1]. However, we have some concerns regarding the criteria used in the study.

First, the authors classified estrogen receptor (ER)-positive/human epidermal growth factor receptor (HER)2-positive tumors as luminal B (LUMB). Although this classification is in accordance with that used in the Carolina Breast Cancer Study [2], the LUMB tumors - as identified by gene expression profiling - were all negative for HER2 [3]. The LUMB tumors are defined as tumors that show low to moderate expression of luminal specific genes, including the ER cluster [3,4]. Extrapolating these findings to routine practical use, one must use semiquantitative immunohistochemistry (Allred-score, Q-score, or an H-score like method) [5-8] to define and distinguish luminal A (LUMA) and LUMB tumors. A large amount of information is lost when one labels a tumor as a mere ER-positive one, because a tumor in which 15% of cells exhibit weak ER staining is biologically different from one that demonstrates strong intensity staining in about 90% of cells. Although the vast majority of ER-positive tumors show strong immunoreactivity, approximately 20% of tumors exhibit variable ER expression. ER expression in breast carcinoma is a continuous variable, which has been demonstrated not only by immunohistochemistry and ligand binding assay, but also by quantitative RT-PCR assays [6,9-11]. Moreover, using data from the NSABP B-14 clinical trial, Baehner and coworkers [12] demonstrated that the greater benefit from tamoxifen is seen in patients with greater ER expression, as determined by RT-PCR.

Although it is difficult to define a cut-off, any ER-positive/HER2-negative tumor showing diffuse and strong ER expression in two-thirds of the tumor (an H-score of 200 or higher) could be considered to be a LUMA tumor and the remainder of ER-positive/HER2-negative tumors could be considered LUMB. Although not the most accurate, this arbitrary cut-off is simple and keeps the category of LUMA tumors as pure as possible using immunohistochemistry. The ER-positive/HER2-positive tumors could similarly be subdivided into LUMA-HER2 hybrid (LAHH) and LUMB-HER2 hybrid (LBHH), based on ER expression levels. The LBHH tumors probably correspond to the originally described luminal C tumors [3]. LAHH tumors definitely exist but do not have a molecular correlate. We believe that this distinction is necessary before studies utilizing surrogate immunohistochemical markers are undertaken, because HER2-positive tumors should be separated from pure luminal tumors, which should be further categorized as LUMA and LUMB tumors.

Second, the authors considered HER2 2+ expression by immunohistochemistry to be a positive finding. Numerous studies have shown that only one-quarter of immunohistochemical score 2+ cases demonstrate HER2 gene amplification by fluorescence *in situ* hybridization [13]. The authors did mention that 'the results of analyses in which HER2 positivity was defined as 3+ were very similar to those presented with a definition of 2+ and 3+'. However, the more important question is about the comparison of '2+ only' cases with '3+ only' cases.

Competing interests

The authors declare that they have no competing interests.

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