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Letter

Luminal B breast tumors are not HER2 positive - authors' response

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See related letter by Bhargava and Dabbs, http://breast-cancer-research.com/content/10/5/404, and see related research article by Tamimi *et al.*, http://breast-cancer-research.com/content/10/4/R67

The letter from Drs Bhargava and Dabbs [1] expressed concern with the immunohistochemical (IHC) criteria we used to define breast cancer molecular phenotypes in our study [2]. Although expression arrays are the 'gold standard' for defining these subtypes, there is sufficient evidence to suggest that the markers we selected provide a reasonable approximation of molecular phenotypes, as determined by gene expression profiling. For a large study such as ours, in which we collected more than 2,800 formalin-fixed, paraffin-embedded tissue samples from cancers occurring over a 20-year period, logistical and technical issues precluded the feasibility of our conducting expression array analyses. The obvious limitation of using IHC markers to define subtypes is that this may result in the misclassification of some tumors.

The criteria for defining molecular subtypes according to IHC markers are not standardized. In general, it is accepted that relative to luminal A cancers, luminal B tumors have lower expression levels of estrogen receptor (ER)/progesterone receptor (PR) and related genes, higher proliferative rates, and are of higher grade. In addition, some tumors defined as luminal B by expression array are human epidermal growth factor receptor (HER)2 positive [3]. However, how best to combine various IHC markers to most closely approximate tumor types as defined by expression profiling remains open to debate. One suggested definition of luminal B cancers is the one we used in our study (ER positive or PR positive and HER2 positive). Other large population-based studies have also utilized the same criteria (or other ER positive/HER2 positive criteria) to define luminal B tumors [4-6].

Despite the potential for misclassification of phenotypes when using IHC, we and others [4,5] have demonstrated that IHC marker defined phenotypes are associated with clinical characteristics similar to those seen in studies using expression array defined subtypes. In our preliminary analyses, using the same subtype definitions, we found that women with luminal B tumors have outcomes intermediate between those with luminal A and other subtypes. These findings are consistent with those in subtypes defined by expression array analysis [3].

Drs Bhargava and Dabbs suggest the use of semiquantitative IHC to define and distinguish luminal A and B subtypes [1]. We agree that utilizing a continuous measure of ER maximizes the use of data and may be more biologically informative. However, quantitative assessment of ER by IHC is subject to error because it is highly influenced by variability in pre-analytic, analytic, and post-analytic factors. Until methodologic studies are conducted that address these issues, it is unclear that our study would benefit from this type of information.

Competing interests

The authors declare that they have no competing interests.

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