TOP2A Amplification in Breast Cancer in the Absence of That of *HER-2*: Myth or Reality?

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TO THE EDITOR

We read with interest the study by Glynn et al. [1] in *The Oncologist* about topoisomerase II α (*TOP2A*) gene amplification in human epidermal growth factor receptor (*HER*)-2[−] breast cancers. The authors reported that, in their series, *TOP2A* amplification levels did not differ significantly according to *HER-2* status by either real-time quantitative polymerase chain reaction (RQ-PCR) or immunohistochemistry microarray and that amplification of *TOP2A* in breast cancer is not confined to *HER-2*⁺ cancers, suggesting that a significant proportion of *HER-2*[−] patients exhibit high levels of *TOP2A*. This is a very important point to consider in their conclusions, because many studies have reported conflicting data on this topic.

HER-2 amplification has consistently been associated with a better tumor response to chemotherapy with anthracyclines than with nonanthracyclines [2–4]. Because *TOP2A* encodes the protein targeted by anthracyclines and *TOP2A* and *HER-2* are closely related on chromosome 17, it was suggested that *TOP2A* was the real biomarker for anthracycline sensitivity. Moreover, some *HER-2*-amplified breast cancers also present *TOP2A* amplification, and although there are conflicting data regarding the prognostic or predictive value of *TOP2A* amplification, most published data, including our recent study [5], show that *TOP2A* amplification is restricted to breast cancers with *HER-2* amplification [6–9]. This observation could be explained by the fact that *HER-2* is the key amplicon driver on chromosome 17. Its amplification leads to chromosome instability and consequently to amplification of different genes along the chromosome, as shown in our study [5].

In the study by Glynn et al. [1], *TOP2A* amplification was

determined by “RQ-PCR of reverse transcribed total RNA extracted from 96 tumor samples.” However, by using this method the authors do not quantify *TOP2A* copy number variation in DNA, but rather *TOP2A* mRNA expression. Then, they compared this mRNA expression and *TOP2A* protein expression. As a consequence, the authors could not conclude about *TOP2A* amplification in *HER-2*⁺ and *HER-2*[−] breast cancers because they confused gene amplification and gene expression.

Gene amplification is a cellular process characterized by the production of multiple copies of a particular gene. It might be related to gene overexpression, but there are other mechanisms leading to protein overexpression via transcriptional and post-transcriptional factors. For instance, in the case of *HER-2*, we and other authors have previously shown that *HER-2* amplification is well correlated with *HER-2* mRNA expression. However, gene amplification and expression are not always correlated [10], as already reported for *TOP2A* [11, 12], and a statement that high mRNA expression is equivalent to gene amplification cannot be considered scientifically valid.

By confusing *TOP2A* amplification and *TOP2A* mRNA overexpression, the article by Glynn et al. [1] could lead to misinterpretations. We thus think that “*TOP2A* amplification” should be changed to “*TOP2A* high transcriptional level” in order to deliver an accurate and clear message.

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