Copy Number Alteration Influences Tumor Microenvironment In Breast Cancer

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Background & objectives

The introduction of therapies targeting genomic instability (e.g. PARP inhibitors) has made it crucial to gain a deeper understanding of the impact of genomic instability on breast cancer. Here we investigate the relationship of genomic instability with tumor microenvironment.

Methods

At our Institution, 1724 patients underwent surgery for invasive breast cancer (January 2012- December 2018). A cohort of 1003 patients was analyzed by immunohistochemistry and grouped based on their molecular subtypes into three copy-number alterations (CNA) patterns identified by Kwei et al (1-2): "simple" with few CNAs, mostly associated with Luminal A pattern of gene expression, "amplifier" with focal high-grade CNAs, involving amplification of one or more chromosomes, usually found in Luminal B and ERBB2-amplified tumors, and "complex" pattern with numerous chromoosomal gains or losses, stretching over multiple regions, most common in triple-negative, basal-like tumors. Stromal tumor-infiltrating lymphocytes (TILs) were assessed according to the recommendations by Salgado et al (3) and semi-quantitatively grouped into a "brisk" (≥5% of immune cells in stromal tissue within the invading border of the tumor) and "non-brisk" category, similar to previously published works (4-6).

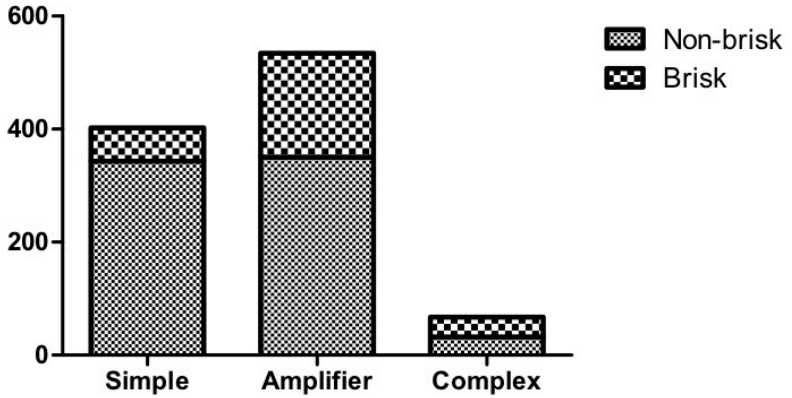
Contingency analysis was performed on GraphPad Prism with the Pearson Chi-Squared test.

Results

In our cohort, "brisk" TILs were found to be significantly associated **(P<0.0001)** with the CNA-associated patterns defined by Kwei et al. Infiltrate was categorized as "brisk" in 15% in tumors belonging to the "simple" pattern (59/402), in 34% of the tumors belonging to the "amplified" pattern (34%), and in 52% of the tumors belonging to the "complex" pattern. Although the use of molecular classification as a surrogate for CNAs is not as precise as the actual genetic analyses, the correspondence between these classes and the CNAs-associated pattern is supported in the literature (2,7).

Conclusion

Our data suggest that genetic instability could have a role in eliciting a strong stromal lymphocytic response in breast cancer, and we postulate this to be due to an increased number of neoantigens contributing to generate and maintain this response. In light of the current and upcoming therapies targeting genomic instability, the identification of surrogate markers to evaluate this instability, including TILs, will become crucial in the understanding and management of breast cancer.



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