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Adjusting Breast Cancer Patient Prognosis with Non-HER2-Gene Patterns on Chromosome 17.

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Abstract

BACKGROUND:

HER2 and TOP2A gene status are assessed for diagnostic and research purposes in breast cancer with fluorescence in situ hybridization (FISH). However, FISH probes do not target only the annotated gene, while chromosome 17 (chr17) is among the most unstable chromosomes in breast cancer. Here we asked whether the status of specifically targeted genes on chr17 might help in refining prognosis of early high-risk breast cancer patients.

METHODS:

Copy numbers (CN) for 14 genes on chr17, 4 of which were within and 10 outside the core HER2 amplicon (HER2- and non-HER2-genes, respectively) were assessed with qPCR in 485 paraffin-embedded tumor tissue samples from breast cancer patients treated with adjuvant chemotherapy in the frame of two randomized phase III trials.

PRINCIPAL FINDINGS:

HER2-genes CN strongly correlated to each other (Spearman's rho >0.6) and were concordant with FISH HER2 status (Kappa 0.6697 for ERBB2 CN). TOP2A CN were not concordant with TOP2A FISH status (Kappa 0.1154). CN hierarchical clustering revealed distinct patterns of gains, losses and complex alterations in HER2- and non-HER2-genes associated with IHC4 breast cancer subtypes. Upon multivariate analysis, non-HER2-gene gains independently predicted for shorter disease-free survival (DFS) and overall survival (OS) in patients with triple-negative cancer, as compared to luminal and HER2-positive tumors (interaction $p=0.007$ for DFS and $p=0.011$ for OS). Similarly, non-HER2-gene gains were associated with worse prognosis in patients who had undergone breast-conserving surgery as compared to modified radical mastectomy ($p=0.004$ for both DFS and OS). Non-HER2-gene losses were unfavorable prognosticators in patients with 1-3 metastatic nodes, as compared to those with 4 or more nodes ($p=0.017$ for DFS and $p=0.001$ for OS).

CONCLUSIONS:

TOP2A FISH and qPCR may not identify the same pathology on chr17q. Non-HER2 chr17 CN patterns may further predict outcome in breast cancer patients with known favorable and unfavorable prognosis.