29th Annual San Antonio Breast Cancer Symposium — Abstract #6111

Relationship between proliferation genes and expression of hormone and growth factor receptors: Quantitative RT-PCR in 10,618 breast cancers

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Background: Many laboratory and clinical studies have suggested that there are important relationships between proliferation genes and hormone and growth factor receptors. To define these relationships using a standardized quantitative RT-PCR assay, we examined the expression of ER, PR, HER2, and proliferation-related genes in a large cohort of breast cancers.

Material and Methods: All tumor specimens successfully examined in the Genomic Health laboratory from January 2004 through March 2006 were included. Quantitative expression for ER, PR, HER2, and the five proliferation genes, CCNB1, Ki-67, MYBL2, STK15, and Survivin, was measured by the pre-specified 21-gene Onco*type* DX™ assay on a scale from 0 to 15 (relative to reference genes), where a one-unit increment is associated with a 2-fold change in expression. The proliferation index (PI), a component of the RS, was calculated as the average of the expression of the five proliferation genes. The provisional RT-PCR cutoff points for ER, PR, and HER2 positivity were 6.5, 5.5, and 11.5, respectively, based on three prior IHC correlation studies. Pearson R correlations were calculated for each comparison.

Results: Among the 10,618 breast cancers, the correlation between ER and PR expression (R = 0.36) was modest. As expected, in ER-negative breast cancer, PR expression was rarely high. However, in ER-positive breast cancer, for any level of ER expression, PR expression ranged from very high to very low. The relationship between ER expression and PI was different for ER-negative and ER-positive breast cancer. For ER-negative breast cancer, the PI tended to modestly increase as the level of ER expression decreased. However, for ER-positive breast cancer, the PI tended to modestly increase as the level of ER expression increased. In contrast, for both ER-negative and -positive breast cancer, the PI tended to decrease as PR increased. Nevertheless, the most striking observation is that the PI was largely independent of ER and PR expression; ER or PR expression accounted for less than 4% of the variance in the PI. Finally, the PI was, on average, higher (1.6-fold) in HER2-positive breast cancer than in HER2-negative breast cancer. However, again, the PI could be high or low for any level of HER2 expression. HER2 expression accounted for less than 2% of the variance in the PI.

Discussion: The expression of the proliferation genes was largely independent of the hormone receptor genes, ER and PR, and the growth factor receptor gene, HER2. Some correlations were observed which, in some cases, differed between ER-negative and ER-positive breast cancer. These results demonstrate the importance of standardized quantitative measurement on a continuous scale, and why contributions of multiple genes are required to characterize invasive breast cancer biology.