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Gene Expression Profiling of Phenotypically-Defined Hormone-Receptor Positive Breast Cancer: Evidence for Increased Transcriptional Activity of the Insulin Growth Factor Receptor Pathway and Other Pathways.

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Background: Approximately 70% of all breast cancers are hormone receptor (HR)-positive tumors that are sensitive to endocrine therapy, but some patients have recurrence despite adjuvant endocrine therapy. We performed an exploratory analysis of gene expression in HR-pos operable breast cancer in order to identify potential novel therapeutic targets and biomarkers associated with recurrence.

Methods: RNA was extracted from primary tumor samples obtained from 776 patients with stage I-III breast cancer treated with adjuvant chemohormonal therapy in trial E2197 (JCO 2008; 26: 4092-4099), of whom 458 had HR-pos disease (defined in a central lab; JCO 2008; 26: 2473). We evaluated RNA expression patterns (by quantitative RT-PCR using a panel of 371 rationally selected genes) in HR-pos cases compared with the HR-neg cases using weighted T statistics, and determined which genes in the HR-pos, HER2-neg group were associated with recurrence (using Cox proportional hazards model score test, Korn's adjusted P value <5% with false discovery rate < 10%).

Results: The top 10 genes exhibiting significantly higher expression in the HR-pos group ($p \leq 6.17e-160$) included *ESR1* plus 5 estrogen regulated genes, confirming our approach of evaluating gene expression in phenotypically-defined subsets. Other pathways that exhibited higher expression in the HR-pos group (among the 40 top genes with higher expression, $p < 8.66e-53$) included the insulin growth factor (IGF) (*IRS1*, *IGFR1*, *IGFB2*), Ras (*RhoB*, *RhoC*, *RAB27B*, *GGPS1*), and HER pathways (*ERBB2*, *ERBB3*, *ERBB4*), and other genes involved in apoptosis (*BCL2*, *BCL2L1*, *BAG1*, *NME6*, *BBC3*), signaling (*MAPK3*, *SEMA3F*, *RXRA*), mismatch repair (*MSH3*), cell cycle regulation (*CCND1*), stress response (*HSPB1*), and tumor suppressor genes (*TP53BP1*, *APC*). These patterns were similar in HER2-pos cases. Pathway analysis (Ingenuity) revealed substantial interconnectivity among these genes, especially between *IGFR1*, *ERBB2/3/4*, *MAPK3*, *BCL2*, and *CCND1*, but not *RhoB/RhoC*. Genes for which increased expression was associated with increased recurrence included those associated with proliferation (*TOP2A*, *AURKB*, *PLK1*) and apoptosis (*BIRC5* - survivin).

Conclusions: This exploratory analysis reveals several pathways that exhibit higher transcriptional expression in HR-pos disease, some of which are also associated with a higher risk of recurrence, suggesting that they may be potential therapeutic targets. This

provides rationale for testing agents currently available in the clinic that inhibit the IGF and other pathways.

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