

Quantitative RT-PCR analysis of ER and PR by Oncotype DX indicates distinct and different associations with prognosis and prediction of tamoxifen benefit

Frederick L Baehner, MD, Drew Watson, PhD, and Steven Shak, MD (Medical, Genomic Health, Redwood City, CA, United States, 94063); Laurel A Habel, PhD, Charles P Quesenberry, PhD, and Angela Capra, PhD (Research, Kaiser Permanente, Oakland, CA, United States, 94612); Gong Tang, PhD, Soonmyung Paik, MD, and Norman Wolmark, MD (Operations, Pathology, Biostatistics, NSABP, Pittsburgh, PA, United States, 15212).

Background: Reports conflict on the relative roles of ER and PR as prognostic and/or predictive factors. To determine whether ER and PR expression as measured by quantitative RT-PCR is prognostic, predictive, or both in ER+ patients, we examined the results for ER and PR in the previously reported NSABP and Kaiser Oncotype DX™ studies.

Material and Methods: Expression was quantified by the 21-gene Oncotype DX assay. ER and PR expression was measured 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 NSABP B-14 study randomized N-, ER+ patients to placebo and tamoxifen. Cox models were used to evaluate the association between gene expression and distant recurrence. The Kaiser study was a case-control study of N- patients diagnosed from 1985-94 at 14 hospitals. Conditional logistic regression was used to evaluate the association between gene expression and breast cancer death.

Results: In NSABP B-14, there were 290 patients treated with tamoxifen and 355 patients treated without tamoxifen; in Kaiser, there were 55 cases and 150 controls treated with tamoxifen and 110 cases and 251 controls treated without tamoxifen who had ER+ tumors. The Pearson correlation of ER and PR expression with each other was modest (R = 0.38 in NSABP and 0.66 in Kaiser). The associations of ER and PR expression with outcome are summarized in the table below.

Study - Treatment	ER HR*	95% CI ER HR	ER <i>p</i> -value	PR HR*	95% CI PR HR	PR <i>p</i> -value
NSABP - No Tam	1.06	0.94, 1.19	0.30	0.89	0.82, 0.97	0.008
NSABP - Tam	0.78	0.69, 0.88	<0.001	0.86	0.76, 0.97	0.007
Kaiser - No Tam	0.92	0.79, 1.07	0.26	0.86	0.77, 0.95	0.005
Kaiser - Tam	0.64	0.46, 0.88	0.003	0.74	0.61, 0.91	0.001

*HR relative to a one-unit increment in expression

In NSABP B-14, the formal test for interaction of quantitative ER with tamoxifen treatment was highly significant (*p* = 0.0005); the interaction of quantitative PR with tamoxifen treatment was not significant (*p* = 0.64).

Discussion: In ER+ patients in both the NSABP B-14 trial and the Kaiser trial, the level of expression of ER is primarily predictive of tamoxifen benefit and is not significantly associated with prognosis in untreated patients. In contrast, the level of PR expression is primarily prognostic and is not predictive of tamoxifen benefit. Although some correlation exists between expression of ER and PR, quantitative expression in individual patients suggests that ER and PR have very different roles in the biology of ER+ breast cancer.