

## ASCO 2005- Abstract #603

### **Gene expression and breast cancer mortality in Northern California Kaiser Permanente Patients: A large population-based case control study.**

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**Background:** The 21 gene Recurrence Score (RS) assay (Oncotype DX) has been validated to quantify the risk of distant recurrence in tamoxifen-treated (tam+) pts with N-, ER+ breast cancer (BC) (Paik et al, NEJM, 2004). The relation between gene expression and BC mortality in a community hospital setting for ER+ tam+ pts, as well as for tam- and ER- pts, was not known.

**Methods:** We conducted a nested case-control study in BC pts diagnosed from 1985-94 at 14 Kaiser hospitals. Eligibility included negative nodes, age < 75 yrs, and no chemotherapy. Cases died of BC prior to 2002. Up to 3 controls were matched to each case on age, race, tam treatment, facility, diagnosis yr, and follow-up time. Using pre-specified methods, archived tumor tissue was analyzed using the RT-PCR 21 gene expression assay and RS algorithm. Pre-specified primary and secondary endpoints were analyzed by conditional logistic regression to estimate the association between gene expression (for RS, proliferation gene group score, and individual genes, including ER and PR) and BC death, while controlling for tumor size, grade, and confounding variables.

**Results:** Among 4964 potentially eligible BC pts, we identified 220 cases and 570 matched controls. Median age was 59 yr (range 28-74); 30.9% were tam+ (mostly after 1988). Median follow-up time was 4.9 yrs for cases (time to death) and 12.9 yrs for controls. RS was significantly associated with BC death in ER+ pts treated with or without tam ( $p=0.002$ ). Gene expression for ER and PR had different associations--ER expression was associated with mortality in the ER+ tam+ pts ( $p = 0.003$ ), but not the ER+ tam- pts ( $p=0.26$ ), and was predictive of tam benefit but not of prognosis. PR was associated with mortality in the ER+ tam- pts ( $0.004$ ), and was strongly prognostic. Among both ER+ tam- pts and ER- pts, those with high proliferation gene group scores had over 6 times the risk of BC death compared to those with low scores ( $p=0.001$ ).

**Conclusion:** A large population-based study from 14 Northern California hospitals demonstrates the Recurrence Score is independently associated with breast cancer mortality, and is both prognostic and predictive.