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HER2 Amplification, Polysomy Status and Breast Cancer Survival in a Large Kaiser Permanente Case-Control Study: Assessment of HER2 by Quantitative Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) and Fluorescence In Situ Hybridization (FISH).

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Background: Polysomy 17 is found in breast cancer and may complicate interpretation of HER2 results. HER2 status by FISH and quantitative RT-PCR were determined in a case-control study that quantitated HER2 mRNA levels in polysomy 17 patients and that examined breast cancer survival in tamoxifen (TAM) treated and untreated patients.

Methods: A Kaiser Permanente nested case-control study was performed in node-negative breast cancer patients diagnosed from 1985-94 who were not treated with chemotherapy. Cases died of breast cancer prior to 2002; up to three controls were matched for each case, with a total of 568 unique patients. HER2 was measured by quantitative RT-PCR by Oncotype DX; pre-defined cutoffs ≥ 11.5 expression units (positive), ≥ 10.7 to < 11.5 expression units (equivocal), and < 10.7 expression units (negative) (each unit represents ~2-fold change in expression). HER2 and polysomy were assessed by FISH (Vysis, Abbott); ratio > 2.2 (positive), 1.8 to 2.2 (equivocal), < 1.8 (negative). Chromosome 17 polysomy was defined as a CEP 17 signal ≥ 3 . Conditional logistic regression explored the association between the HER2/Polysomy subgroups and risk of breast cancer death.

Results: Median age at dx was 59 yrs, 30.9% were TAM treated and median time to death was 59 months. 12% (67/568) of patients were HER2 positive by RT-PCR and 11% (60/568) were HER2 positive by FISH. By ASCO/CAP guidelines, concordance for HER2 by central FISH and central RT-PCR was 97% (95% CI: 96%, 99%). HER2 positivity by either method was weakly prognostic; HER2 positive patients had increased odds of dying from breast cancer compared to HER2 negative patients (by FISH (OR=1.95, 95% CI=1.19-3.19) and RT-PCR (OR=1.72, 95% CI=1.04-2.84)). Similar results were obtained in TAM-treated and untreated groups separately. Seventy-one (12.5%) patients showed polysomy 17. 33% of FISH positive patients were polysomy 17 (20/60) and 19 of the 20 were RT-PCR HER2 positive (Table). The majority of FISH negative polysomy 17 cases were RT-PCR HER2 negative (32/49) but rare cases (4/49) were RT-PCR HER2 positive. Compared to chromosome 17 eusomic patients, HER2 positive patients with polysomy 17 had 2.77 (95% CI: 1.21, 6.33) times the odds of dying from breast cancer; HER2 positive, chromosome 17 eusomic patients had 1.78 (95% CI: 0.97, 3.25) times the odds; and HER2 negative, polysomy 17 patients had 1.50 (95% CI: 0.83, 2.72) times the odds.

Incidence of Polysomy 17 by HER2 Status (FISH and RT-PCR)				
HER2	Central FISH	Central FISH	Central FISH	Total RT-

	positive	equivocal	negative	PCR
RT-PCR positive	19/55 (35%)	1/1 (100%)	4/11 (36%)	24/67 (36%)
RT-PCR equivocal	0/4 (0%)	1/5 (20%)	13/79 (17%)	14/88 (16%)
RT-PCR negative	1/1 (100%)	0/4 (0%)	32/408 (8%)	33/413 (8%)
Total FISH	20/60 (33%)	2/10 (20%)	49/498 (10%)	71/568 (13%)

Conclusion: HER2 amplification with polysomy was common. FISH negative polysomy 17 cases were rarely RT-PCR HER2 positive. While differences were not statistically significant, HER2+/polysomy 17 patients tended to have the worst prognosis, followed by HER2+/eusomic, HER2-/polysomy 17, and HER2 negative eusomic pts whether HER2 status was measured by FISH or RT-PCR.

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